NOVARTIS

Clinical Development & Medical Affairs

Nilotinib (AMN107)

Protocol No. CAMN107DDE06 /NCT00756509

An open-label, multi-center, single-arm study to evaluate the efficacy of nilotinib in adult patients with metastatic or unresectable gastrointestinal stromal tumors in first line treatment

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Signature page for Novartis

Compound name: AMN107 (Nilotinib)

Protocol number: CAMN107DDE06

Approved by the following:

Dr. [redacted] (Principal Investigator)	Signature	Date
Dr. [redacted] ([redacted], Novartis)	Signature	Date
[redacted] (Study Lead, Novartis)	Signature	Date
[redacted] (Study Statistician, Novartis)	Signature	Date

Signature page for investigators

Compound name: AMN107 (Nilotinib)

Protocol number: CAMN107DDE06

I have read this protocol and agree to conduct this trial in full accordance with the protocol and the Declaration of Helsinki.

I have read and I understand the information in the Investigators' Brochures or Package Inserts, including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of investigator	Signature	Date

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/SGPT
ANC	Absolute neutrophil count
AP	Acute phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
ATP	Adenosine triphosphate
AUC	Area under the curve
bid	bis in diem/twice a day
BCR	Breakpoint cluster region gene
Bcr-Abl	A fusion gene of the BCR and ABL genes
BC	Blastic crisis
BUN	Blood urea nitrogen
CCyR	Complete cytogenetic response
CBC	Complete blood count
CHR	Complete hematologic response
CML	Chronic Myelogenous Leukemia
CP	Chronic phase
CR	Complete response
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	NCI common terminology criteria for adverse events
CYP	Cytochrome P450
DNA	Deoxyribose nucleic acid
ECG	Electrocardiogram
CRF	Case report form
EDC	Electronic data capture
EDM	Electronic data management
ECG	Electrocardiogram
EOS	End of study
FDA	Food and drug administration
FDG-PET	[18F]-flourodeoxyglucose-positron emission tomography
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumor
GLP	Good laboratory practice
HES	Hypereosinophilic syndrome
Hgb	Hemoglobin
HPLC	High pressure (performance) liquid chromatography
IC50	Concentration that inhibits function by 50%
IEC	Independent Ethics Committee

IMS	Integrated Medical Safety
IRB	Institutional Review Board
LC-MS/MS	Liquid chromatography – tandem mass spectrometry
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
mg/m^2	Milligrams per square meter
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
MUGA	Multiple uptake gated acquisition scan
PET/CT	Combination PET and CT scanner
PDGFR	Platelet derived growth factor receptor
PFS	Progression free survival
PG	Pharmacogenetic
PI3-kinase	Phosphoinositide 3-kinase
PK	Pharmacokinetic
PR	Partial response/ remission
REB	Research Ethics Board
SAE	serious adverse event
SCF	Stem cell factor
SD	Stable disease
SM	Systemic mastocytosis
SC	Steering committee
SOP	Standard Operating Procedure
SST	Serum separator tube
SUV	Standardized Uptake Value
TK	Tyrosine kinase
TNF	Tumor necrosis factor
TTP	Time to tumor progression
ULN	Upper limit of normal
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell
WOCBP	Women of child bearing potential
WHO	World Health Organization
WNL	Within normal limits

Amendment 5

Amendment rationale

The recruitment of this study has been completed (LPFV 16-Jul-2014) and 44 patients have been enrolled. As of 26-Nov-2018, 5 patients are ongoing in the study.

On May 5, 2011, Novartis took the decision to discontinue the ongoing clinical trials with nilotinib in GIST. This decision was based on the results of the first interim analysis for futility as specified in the ENESTg1 protocol CAMN107G2301 which has shown, that nilotinib in GIST is unlikely to demonstrate superiority to imatinib in progression free survival, the primary study endpoint. The independent Data Management Committee also reported that there were no safety issues identified in either arm of this trial. Patients who are receiving nilotinib and considered by the investigators to be deriving benefit should have the option to remain on the medication. For patients benefiting from nilotinib treatment of the Novartis-Sponsored studies CAMN107G2301 and CAMN107DDE05, the enrollment of the study CAMN107DDE06 has being re-opened in order to ensure continued access to nilotinib after closing of these studies.

Nilotinib (Tasigna®) is approved by US Food and Drug Administration (FDA) and European Commission (EC) and well established for the treatment of adult and pediatric patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP), adult patients with CP and accelerated phase (AP) Ph+ CML resistant to or intolerant to at least one prior therapy including imatinib and for the treatment of pediatric patients with Ph+ CML-CP resistant or intolerant to prior therapy including imatinib. The safety profile and the pharmacokinetics in human are extensively investigated (see latest nilotinib Investigator's Broschure).

The primary purposes of the amendment are:

- To remove the pharmacokinetic analysis from the protocol. The pharmacokinetic of nilotinib have been explored very well in human and new results are not expected from further analysis of pharmacokinetic samples.
- To reduce the burden to the patients, the visit schedule will be adapted to every 6 month. Additionally visits between the 6-month-period are at the discretion of the investigator and/or local physician and will be done as a local routine.

Additional changes implemented with this amendment are:

- To replace the authors [redacted] with [redacted] as Principal Investigator, of [redacted] with [redacted] as [redacted], of [redacted] with [redacted] as Study Lead, of [redacted] with [redacted] as Statistician and to delete [redacted] as [redacted]
- To update the background, pharmacokinetics and safety information
- To update the comprehensive list of reference of agents that prolong QT interval
- To update the list of cytochrome P450 3A4 isoenzym inducers and inhibitors and to add substrates

- To correct protocol inconsistencies

Changes to the protocol:

Changes to the specific sections of the protocol are shown in the track changes version of the protocol using strike through red font errors for deletions, red (underline) for insertions.

Authors:

- Replacement of [redacted] with [redacted] as Principal Investigator, of [redacted] with [redacted] as [redacted], of [redacted] with [redacted] as Study Lead, of [redacted] with [redacted] as Statistician and to delete [redacted] as [redacted]

Sections 1.2, 1.2.2:

- Update on the nilotinib overview and pharmacokinetics and the safety information of the protocol according to the Investigator's Brochure v 14.0, safety cut-off 31 January 2018.

Section 3.2:

- Deletion of assessment of nilotinib pharmacokinetics as a secondary objective.

Section 4:

- Update on the current trial status.

Section 5.2:

- Insertion of a new link as reference for medications that may prolong QT interval.

Section 6.2:

- Clarification on drug supply and the usage of commercial packs provided by Novartis.

Section 6.6.3:

- Insertion of new links as reference for medications that may prolong QT interval and interact with CYP3A4.

Section 6.6.4:

- Specification that collection of survival information will end at 28 day safety follow evaluation.

Table 7.1:

- Update of the table to delete pharmacokinetic sampling, to delete Choi criteria assessment, to extend the visit schedule for patients in Follow-up phase up to 6

month and to specify EoT procedure and safety follow up following the last study drug intake.

Section 7.4

- Specification that imaging will be done according to the visit schedule during the Follow up phase.

Section 7.5.5

- Clarification on protocol.

Section 7.5.7

- Deleted Section: Pharmacokinetics
- Update of address for pathological review.

Section 10.5.4

- Deleted section: Pharmacokinetics

Reference section:

- Update of the protocol references.

Appendix 1:

- Deleted section: Preparation & Shipping of Pharmacokinetic Samples

Post-text supplement 2:

- Insertion of a new link as reference for medications that may prolong QT interval.

Post-text supplement 4:

- Deleted post-text supplement 4: Choi criteria and Table 11-4 Response criteria
- Update of the lists of CYP3A4 inducers and inhibitors and added a list of CYP3A4 substrates.

IRBs/IECs

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.

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.

1. Background

1.1 Overview of Gastrointestinal stromal tumors (GIST)

Gastrointestinal stromal tumors (GIST) are mesenchymal neoplasms that are thought to arise from the interstitial cells of Cajal or their mesenchymal stem cell precursor. GISTs are positive for the CD117 antigen, an epitope of the KIT receptor tyrosine kinase (TK), in almost 100% of cases (Corless et al 2004). KIT is a 145-kD transmembrane glycoprotein with tyrosine kinase activity that serves as a receptor for the stem cell factor (SCF). Binding of SCF to KIT results in receptor homodimerization, activation of tyrosine kinase activity and phosphorylation of a variety of substrates involved in intracellular signal transduction pathways (Tosoni et al 2004). GISTs are most commonly found in the stomach (52%), followed by the small intestine (25%), large intestine (11%) and esophagus (5%). A small percentage (7%) of tumors arise from the omentum, mesentery and peritoneum. The clinical presentation of GIST varies, ranging from small silent lesions found during surgery to larger lesions causing abdominal pain and acute hemorrhage from tumor rupture, bowel obstruction and/or perforation. Several observations indicate some differences in the biology of GISTs depending on their site of origin, however, the actual clinical course is difficult to predict, and even small lesions (< 2 cm in diameter) have an unpredictable malignant potential. Many authors have accepted tumor size and mitotic rate as morphologic criteria for predicting tumor behavior. Efforts are currently directed to define more objective prognostic parameters including genetic biomarkers (Singer 2002, Heinrich 2003a, Tosoni 2004).

Activating mutations of KIT are the characteristic pathogenic feature of these tumors, being present in up to 92% of GISTs (Heinrich et al 2002). Recent studies have reported a small subgroup of KIT-negative GISTs (Tosoni 2004, Corless 2004). Among the GISTs without KIT mutations, a subgroup has mutations in the platelet-derived growth factor receptor A (PDGFRA) and another subgroup lack identified mutations. KIT Exon 11 mutations, in the form of frame deletions, missense mutations, and internal tandem duplication have been found in 57-77% of cases. In 3-18% of cases, mutations, mainly duplications, have been found in KIT exon 9. Point mutations in exons 13 and 17 are very rare (2-4% of all GISTs). Heinrich et al (2003b) have recently reported activating mutations in the PDGFRA (exons 12 and 18) in 35% of GISTs without KIT mutations. PDGFRA mutations were absent in tumors harboring known KIT mutations and KIT mutant tumors lacked PDGFRA mutations suggesting that PDGFRA and KIT mutations give rise to alternative and mutually exclusive oncogenic mechanisms in GISTs. Moreover, the same activated signal transduction pathways were present in KIT and PDGFRA-mutant tumors further confirming that both genes play an important role in the development of GISTs.

The mainstay of therapy for GISTs is surgical resection, however, recurrence is almost inevitable in high-risk tumors and secondary surgery or other salvage therapy has yielded poor outcome. The median survival for patients with unresectable or metastatic GIST is approximately 20 months, and for patients with local recurrence it is 9 to 12 months. Responses to chemotherapy have been at best 5%. The introduction of

imatinib has dramatically changed the prognosis of these patients yielding response rates between 41% and 71% and an overall clinical benefit (tumor responses plus stable disease) ranging between 73% and 90% (Demetri 2002, van Oosterom 2002, Benjamin 2003, Verweij 2003, Verweij 2004). Imatinib is the first-line therapy for metastatic GIST with a median progression free survival

(PFS) reported between 18 months (Phase III) and 29 months (Phase II) and a median overall survival of 57 months (Verweij 2004, Blanke 2008a, Blanke 2008b, Bertucci 2012).

During the consensus conference on GIST management (Blay et al 2006), the recommended option in patients progressing on imatinib 400 mg daily was to increase the dose of imatinib. Dose escalation of imatinib from 400 mg to 600 mg and 800 mg for patients who progress during therapy with imatinib 400 mg has been approved in Europe. Two very similar, large Phase III studies (Verweij 2003, Rankin 2004), comparing imatinib 400 mg daily and 800 mg daily, showed similar response rates with the two imatinib doses. Both trials reported superior progression free survival (PFS) in the 800 mg arm, one of them reaching statistical significance (median PFS of 22 months versus median PFS not reached, p=0.02) (Verweij et al 2003), while, the other was not statistically significant (median PFS of 22 months versus 27 months, p=0.13) (Rankin et al 2004). In both of these studies, patients initially randomized to receive imatinib 400 mg daily could cross-over to 800 mg daily upon disease progression. In the European trial, 133 out of 247 patients who had progressive disease crossed-over to imatinib 800 mg daily (Zalcberg et al 2005). Three patients achieved a partial response (2.3%) and 36 patients had stable disease (27%). The median PFS after cross-over was 81 days. Similar results were observed in the US study in which 84 out of 164 patients treated with 400 mg imatinib and having progressive disease crossed-over to the 800 mg arm (Rankin et al 2004). Five of these patients achieved a partial response (7%) and 20 patients had stable disease (29%). Median progression-free survival and overall survival for patients who crossed over were 4 months and 19 months, respectively. Imatinib was well tolerated across all studies up to a dose of 800 mg daily with the main adverse effects being nausea, vomiting, edema and skin rash. An adverse event observed particularly in GISTs patients was gastrointestinal hemorrhage, potentially related to tumor necrosis induced by imatinib.

1.2 Overview of nilotinib

Nilotinib is a second generation inhibitor of the Bcr-Abl tyrosine kinase which, like imatinib, targets the causative abnormality of chronic myelogenous leukemia (CML). Nilotinib is an ATP-competitive inhibitor of the protein tyrosine kinase activity of Bcr-Abl, which prevents the activation of Bcr-Abl dependent mitogenic and anti-apoptotic pathways (e.g. PI-3 kinase and STAT5), leading to the death of the Bcr-Abl phenotype. In addition, nilotinib inhibits the PDGF-receptor tyrosine kinases including FIP1L1-PDGFRα tyrosine kinase, which is often associated with HES and chronic eosinophilic leukemia (CEL), and TEL-PDGFRβ which causes chronic myelomonocytic leukemia

(CMML), as well as the stem cell factor receptor c-Kit tyrosine kinase, which is often associated with GIST and SM.

The activity of nilotinib on c-Kit autophosphorylation has been investigated using GIST882 cells, a human cell line expressing constitutively activated c-Kit (CD117) derived from a patient with GIST, and in Ba/F3 cells engineered to express the D816Y and D816V mutant forms of KIT. Nilotinib potently reduced c-Kit autophosphorylation in GIST cells with a mean IC50 of 202 nM, similar to that of imatinib. The compound was less potent against D816Y and D816V mutant autophosphorylation in Ba/F3 cells, with mean IC_{50} values of 480 and 2500 nM respectively. Experiments conducted in GIST cell lines carrying mutations sensitive and resistant to imatinib (GIST882, GIST430 and GIST48) have shown that nilotinib inhibits proliferation of these cell lines more potently than imatinib (Dileo et al 2006). Moreover, studies investigating the cellular uptake of nilotinib in comparison with imatinib have revealed that nilotinib intracellular concentrations are 7- and 10- fold higher that those of imatinib in GIST882 and GIST GDG1 cell lines respectively (Prenen et al 2006).

In *in vitro* assays, nilotinib has been shown to interact with CYP2C9, CYP2C8, CYP2D6, and CYP3A4. Because of the inherent risk of either reduced activity or enhanced toxicity of the concomitant medication and/or nilotinib, medications known to interact with these cytochrome P450 isoenzymes should be used with caution (Post-text supplement 5). In particular concomitant use of CYP3A4 inhibitors should be avoided if at all possible.

Clinical Pharmacokinetics

Nilotinib is metabolized by the liver, primarily via CYP3A4. Thus strong inhibitors or inducers of CYP3A4 can significantly alter the pharmacokinetics and systemic exposure of nilotinib in humans. In addition, nilotinib exhibits moderate inhibitory effect on CYP3A4, which may increase the exposure of sensitive CYP3A4 substrates. Unchanged nilotinib represents the predominant systemic circulating component (approximately 88% of the total drug-related serum exposure). The terminal elimination half-life of nilotinib was estimated to be approximately 17 hours.

Race was assessed as a covariate on the bioavailability or clearance of nilotinib in the population pharmacokinetic analysis which included a total of 550 patients. No significant differences were observed in nilotinib pharmacokinetics across various race groups, e.g. Caucasian (n=348 patients), Black (n=23 patients), Asian (n=138 patients) and other races (n=41 patients) [Modeling report CAMN107A2303]. These findings are consistent with the previous observations in patients with imatinib resistant or intolerant CML [Study CAMN107A2101 PopPK] and the ethnic insensitivity analysis conducted for the original Tasigna® submission. Population pharmacokinetics (PK) analysis also suggested that male patients had an approximately 10% lower bioavailability or 10% lower systemic exposure than female Patients. However, since the observed extent of the difference is relatively small, such a sex effect is unlikely to be clinically meaningful for nilotinib therapy. Other demographic variables, such as age and body weight did

not significantly affect nilotinib PK. Thus, patient demographics are not a clinically important factor contributing to interpatient variability in nilotinib PK and exposure.

Impaired renal function is not expected to influence nilotinib PK, since neither nilotinib nor its metabolites are renally excreted.

Compared to healthy subjects with normal hepatic function, nilotinib AUC0-∞ was increased by 35% in both the mild (Child-Pugh class A, score 5-6) and moderate (Child-Pugh class B, score 7-9) impairment groups, and by 19% in the severe impairment group. The mean T1/2 of nilotinib was similar between the mild hepatic impairment and non-impaired control groups (approximately 15.1 and 16.0 hours, respectively), but was prolonged in the moderate and severe hepatic impairment groups (to 21.6 hours and 32.4 hours, respectively) (Yin 2009).

Bioavailability of nilotinib is reduced following gastrectomy. Population PK analysis from [CAMN107A2201] estimated that the relative bioavailability of nilotinib was reduced by approximately 48% and 22% in patients who had undergone total or partial gastrectomy, respectively. The extent of decrease in nilotinib absorption due to partial gastrectomy is small, and thus its impact on nilotinib therapy is expected to be minor.

For additional nilotinib clinical pharmacokinetics information, please refer to the latest nilotinib [Investigator's Brochure].

1.2.1 Clinical experiences with nilotinib

A Phase I/II study of nilotinib (CAMN107A2101), is currently taking place in adult patients with imatinib-resistant CML in CP (chronic phase), AP (accelerated phase) or BC (blastic crisis), relapsed/refractory Ph+ ALL, and other hematological malignancies.

A total of 321 CML-CP patients (70.4% imatinib-resistant, 29.6% were imatinib-intolerant) in the Phase II study [CAMN107A2101E2] were evaluated for efficacy. Patients were treated with nilotinib 400 mg BID (total daily dose of 800 mg).

At 24 months data cut-off, 124 (38.6%) patients were ongoing and 197 (61.4%) had discontinued treatment. The reasons for discontinuation were mainly due to AEs (61 patients, 19.0%) and disease progression (88 patients, 27.4%). For additional safety data, please refer to the IB version 9. Nilotinib induced a major and complete cytogenetic response in 51.4% and 36.8% of patients, respectively. These responses were durable: an estimated 77% and 85% of patients with MCyR and CCyR, respectively, maintained response at 24 months.

A Phase I study of nilotinib alone and in combination with imatinib [CAMN107A2103] was performed in adult patients with imatinib-resistant GIST. The study showed that nilotinib alone or in combination with imatinib was well tolerated and showed clinical activity in the studied patient population.

The efficacy of nilotinib in patients with newly diagnosed Ph+ CML-CP has been evaluated in a phase III multi-center open label, randomized study

(CAMN107A2303/ENESTnd) comparing nilotinib to imatinib in adult patients with newly diagnosed CML-CP. This study is ongoing and showed continuing superiority of nilotinib vs. imatinib at 12, 24, 36, and 48 months follow-up in terms of cytogenetic and molecular responses, as well as in reduction of progression to AP/BC. A total of 846 newly diagnosed CML-CP patients were randomized into the study of which 643 patients were still receiving treatment as of the 48 month cut-off date (162 patients (57.2%) in the imatinib arm, 186 patients (66.0%) in the nilotinib 300 mg b.i.d arm and 195 patients (69.4%) in the nilotinib 400 mg b.i.d arm).

At the time of the 48 month cut-off date, the time on treatment was comparable between the treatment groups, with a median of about 48 months in all groups. Most patients (>98%) experienced at least one adverse event (AE). The most frequently affected system organ class (SOC) in the nilotinib groups, were skin and subcutaneous tissue disorders and GI disorders.

In the imatinib group, the most frequently affected SOCs were GI disorders and musculoskeletal and connective tissue disorders. The highest incidence of combined AEs/abnormal laboratory values leading to study discontinuation was observed in the nilotinib 400 mg b.i.d. arm (46 patients, 16.4%), followed by the imatinib arm (33 patients, 11.7%) and the nilotinib 300 mg bid arm (28 patients, 9.9%).

A Phase III study of nilotinib vs. best supportive care (with or without imatinib or sunitinib) was performed [CAMN107A2201].

A total of 248 patients with third-line unresectable and/or metastatic gastrointestinal stromal tumors (GIST) were randomized in a 2:1 ratio to the nilotinib arm (165 patients) or to the control arm (83 patients). The control arm included three treatment options (to be selected by investigators): best supportive care (BSC) only, BSC plus imatinib (BSC+I), and BSC plus sunitinib (BSC+S).

Patients whose tumors had not progressed at the completion of the core study (i.e., after 174 events had occurred) were eligible for roll-over to the extension study. All patients continued to be treated as per their assigned treatment arm until they experienced disease progression.

Therefore, patients entering the extension study on the control arm were permitted to cross over to nilotinib only upon documented disease progression according to RECIST criteria based on investigators assessment.

This study was completed on June 20, 2011. Median duration of exposure to nilotinib treatment was 127 days for nilotinib and 82 days for the control arm. Among nilotinib patients, 63 (38%) were treated for > 6 months, including 43 (26%) patients for > 9 months.

Median duration of exposure for patients crossing over to nilotinib in the extension study was 89 days. The majority of patients (82%) were treated with nilotinib after crossover for less than 6 months. The duration of nilotinib exposure after crossover ranges from 1 to 1273 days.

In the core study result, for the primary efficacy variable of PFS based on blinded central radiology review, there was no significant difference between the arms in the

distribution of time to PFS event (median 109 and 111 days, respectively; log-rank test p=0.5555). Based on the local review, there was a highly significant difference in PFS based on local radiology assessments in favor of nilotinib. Median PFS was 119 days in the nilotinib arm vs. 70 days in the control arm (p=0.0007, log-rank test). Since the primary endpoint for the PFS evaluation was based on the independent radiological review and no additional independent radiological review was conducted after the cut-off date reported in the Core study CSR (27-Jun-2008), there was no further update on the PFS for the Core study.

OS was not statistically significant between the two treatment arms (p=0.3547, log-rank test).

A total of 217 deaths were reported: 142 (86.1%) in the nilotinib arm and 75 (90.4%) in the control arm. The median OS was 361 days in the nilotinib arm vs. 300 days in the control arm.

The OS rate at 12 months was 49.0% for nilotinib arm vs. 43.9% for control arm.

In study [CAMN107G2301] patients with unresectable and/or metastatic GIST who have either not received prior therapy with a TKI or who have recurrent GIST after stopping adjuvant therapy, were randomized to either nilotinib or imatinib therapy (Table 5-3). The primary objective of this study is to compare PFS of nilotinib and imatinib when used as initial therapy in this patient population.

Based on data as of November 11, 2010, a planned interim analysis for futility was conducted.

The results were reviewed by an independent Data Monitoring Committee (DMC) on April 4, 2011. The DMC observed that the futility boundary had been exceeded and therefore concluded that the study was highly unlikely to meet its primary endpoint. DMC's recommendation was therefore to stop recruitment. Accrual was stopped on April 8, 2011. As a result, the development program of nilotinib in GIST was closed.

Nilotinib is currently approved for the treatment of adult patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia in chronic phase and accelerated phase resistant to or intolerant to at least one prior therapy including imatinib and for the treatment of adult patients with newly diagnosed Ph+ CML in CP.

Tasigna is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase.

1.2.2 Adverse reactions from clinical studies

Adverse reactions reported as more than an isolated case are listed by system organ class and by frequency in Table 1-1. Frequency categories are defined using the following CIOMS III frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare

(<1/10,000) and not known (cannot be estimated from the available data). Information in tables below was taken from the Investigator's Brochure v. 9.0.

In general, the safety profile in GIST patients was similar to that in CML patients, with the exception of a lower incidence of hematological toxicity in GIST patients.

Table 1-1 Adverse reactions from clinical studies

Most frequent drug-related adverse events (more than 5%) at 24-months in CML-AP and -CP patients (Study 2101 E1 and E2)

Preferred Term	2101E11 All grades CML-AP N=137 n (%)	2101E21 All grades CML-CP N=321 n (%)
Any event	**120 (87.6)**	**304 (94.7)**
Thrombocytopenia	52 (38.0)	90 (28.0)
Neutropenia	31 (22.6)	48 (15.0)
Rash	29 (21.2)	99 (30.8)
Anemia	24 (17.5)	42 (13.1)
Pruritus	24 (17.5)	84 (26.2
Lipase increased	18 (13.1)	41 (12.8)
Fatigue	14 (10.2)	65 (20.2)
Constipation	13 (9.5)	43 (13.4)
Diarrhea	13 (9.5)	39 (12.1)
Leukopenia	13 (9.5)	13 (4.0)
Muscle spasms	13 (9.5)	24 (7.5)
Nausea	13 (9.5)	79 (24.6)
Alopecia	12 (8.8)	27 (8.4)
Myalgia	12 (8.8)	33 (10.3)
Blood bilirubin increased	11 (8.0)	22 (6.9)
Headache	11 (8.0)	57 (17.8)
Hyperbilirubinemia	11 (8.0)	23 (7.2)
Abdominal pain	10 (7.3)	17 (5.3)
Pyrexia	9 (6.6)	13 (4.0)
Anorexia	8 (5.8)	23 (7.2)
Pain in extremity	8 (5.8)	17 (5.3)
Arthralgia	7 (5.1)	24 (7.5)
Hypophosphatemia	7 (5.1)	8 (2.5)
Peripheral edema	7 (5.1)	20 (6.2)
Vomiting	5 (3.6)	41 (12.8)
Alanine aminotransferase increase	5 (3.6)	34 (10.6)
Bone pain	5 (3.6)	24 (7.5)
Erythema	2 (1.5)	23 (7.2)
Asthenia	5 (3.6)	21 (6.5)
Aspartate aminotransferase increase	4 (2.9)	20 (6.2)

Dry skin	5 (3.6)	20 (6.2)
Dyspnea	0 (0.0)	17 (5.3)
Weight decreased	3 (2.2)	17 (5.3)

AP = accelerated phase, CML = chronic myeloid leukemia, CP = chronic phase,

[1] The source used for 24-month 2101E1 data (cut-off 29-Aug-2008) and 24-month 2101E2 data (cut-off 20-Apr-2008)

Source: [CAMN107A2101E1] and [CAMN107A2101E2 CSR].

1.2.2.1 Ischemic Vascular and Ischemic Cardiovascular Events Reported for CAMN107A2303 (ENESTnd Study)

Newly-diagnosed or worsened Ischemic Vascular and Ischemic Cardiovascular Events such as Ischemic Heart Disease (IHD), Ischemic Cerebrovascular Events (ICVE) or Peripheral Artery Occlusive Disease (PAOD) have occurred in a relatively small number of CML-CP patients while on study medication. However, such events have been reported with higher frequency on the nilotinib treatment arms compared with the imatinib treatment arm. Up to the data cut-off for the 60 Month analysis (30-Sep-2013), the number of patients reported with events is as follows:

- Nilotinib 300 mg BID: IHD, 11 (3.9%); ICVE, 4 (1.4%); PAOD, 7 (2.5%)

- Nilotinib 400 mg BID: IHD, 24 (8.7%); ICVE, 9 (3.2%); PAOD, 7 (2.5%)

- Imatinib 400 mg QD: IHD, 5 (1.8%); ICVE, 1 (0.4%); PAOD, 0 (0.0%)

The majority of reported ischemic vascular and ischemic cardiovascular events were in patients with associated risks (e.g., advanced age, hypertension, hyperlipidemia, hypercholesterolemia, smoking, diabetes mellitus, pre-existing peripheral vascular disease).

1.2.2.2 ECG QT prolongation

Nilotinib has an IC_{50} value of 0.13 μM in the hERG channel assay indicating the potential for QT prolongation of nilotinib.In the Phase III study in newly diagnosed Ph+ CML-CP patients the change from baseline in mean time-averaged QTcF interval at steady-state observed in the nilotinib 300 mg BID group was 6 ms. At the recommended dose of 300 mg BID no patient had an absolute QTcF of >480 ms and no events of Torsade de Pointes were observed.

In the Phase II study in imatinib-resistant or intolerant CML patients in chronic and accelerated phase, treated with nilotinib 400 mg BID, the change from baseline in mean time-averaged QTcF interval at steady-state was 5 and 8 ms, respectively. QTcF of >500 ms was observed in 4 patients (<1% of these patients).

In a healthy volunteer study with exposures that were comparable to the exposures observed in patients, the time-averaged mean placebo-subtracted QTcF change from baseline was 7 ms (CI ± 4 ms). No subject had a QTcF >450 ms. In addition, no

clinically relevant arrhythmias were observed during the conduct of the trial. In particular, no episodes of torsade de pointes (either transient or sustained) were observed.

Clinically meaningful prolongation of the QT interval may occur when nilotinib is inappropriately taken with food, and/or strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT. Therefore, co-administration with food must be avoided and concomitant use with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT should be avoided. The presence of hypokalemia and hypomagnesemia may place patients at risk of developing QT prolongation.

Known risk factors for QT prolongation are bradycardia, left ventricular failure, electrolyte abnormalities (hypokalemia, hypocalcemia), congenital long QT syndrome, heart disease, female gender, genetic variants, drug interactions (concomitant use of 2 drugs that prolong QTc interval).

1.2.2.3 Sudden deaths

In clinical trials, uncommon cases (0.1 to 1%) of sudden death have been reported in patients in patients with imatinib-resistant or intolerant CML in chronic and accelerated phase receiving nilotinib with a past medical history of cardiac disease or significant cardiac risk factors. Comorbidities in addition to the underlying malignancy were also frequently present as were concomitant medications. Ventricular repolarization abnormalities may have been contributory factors. Based on post-marketing exposure in patient-years, the estimated reporting rate for spontaneous reports of sudden death is 0.01% per patient-year. No cases of sudden deaths have been reported in the newly diagnosed Ph+ CML-CP Phase III study [CAMN107A2303].Safety in GIST patients

In general, the safety profile in GIST patients was similar to that in CML patients, with the exception of a lower incidence of hematologic toxicity.

1.2.2.4 Safety in Study CAMN107A2201

In the phase III study [CAMN107A2201], the median (mean) dose intensity was 800 mg/day (749.6 mg/day) for nilotinib, 800 mg/day (625.8 mg/day) for imatinib and 30.1mg/day (33.2 mg/day) for sunitinib.

Adverse events were reported in 242 patients (97.6%). Adverse events reported most frequently affected the gastrointestinal system (197 patients, 79.4%), with an incidence similar between the nilotinib arm (129 patients, 78.2%) and the control arm (68 patients, 81.9%).

Study drug-related AEs were reported in a total of 177 (71.4%) patients: 126 (76.4%) in the nilotinib arm and 51 (61.4%) in the control arm. The most commonly reported study drug related AEs were asthenia, nausea and fatigue in the nilotinib arm and nausea, peripheral edema and vomiting in the control arm. Overall 43 (17.3%) patients reported Grade 3 or 4 study drug-related AEs: 32 (19.4%) in the nilotinib arm and 11 (13.3%) in the control arm. Asthenia (5 patients, 3.0%) and lipase increase (4 patients, 2.4%) were the most frequently reported Grade 3 or 4 study drug-related AEs in the

nilotinib arm and anemia (4 patients, 4.8%) and neutropenia (3 patients, 3.6%) was the most frequently reported Grade 3 or 4 study drug-related AE in the control arm. All other Grade 3 or 4 study drug-related AEs occurred with a frequency of less than 2% in the nilotinib or control arms. The pattern and incidence of AEs, SAEs, other clinically significant AEs and deaths, was as expected in the population studied. Overall adverse events and SAEs most commonly affected the gastrointestinal system. Nearly all deaths were due to disease progression. The percentage of patients with AE, study drug-related SAEs, Grade 3 or 4 AEs, SAEs, study drug-related SAEs and AEs associated with discontinuation was slightly higher in the nilotinib arm compared to the control arm.

1.2.2.5 Summary of safety

The currently approved dose of nilotinib is 400 mg BID for imatinib-resistant/-intolerant Ph+ CML patients and 300 mg BID for newly diagnosed Ph+ CML patients.

While AEs are common in CML, they are generally mild to moderate, reversible, and manageable with dose interruption and/or dose reduction. The most common grade ¾ toxicities are hematologic, which are not unexpected in the CML population, and are generally manageable. Hematotoxicity is more frequent in patients with imatinib-resistant or -intolerant CML and in particular in patients with CML-AP and CML-BC. The most commonly reported non-hematologic adverse reactions in patients with newly diagnosed Ph+ CML-CP, resistant or intolerant Ph+ CML-CP, or resistant or intolerant Ph+ CML-AP are rash, pruritus, headache, nausea, fatigue, myalgia, nasopharyngitis, constipation, diarrhea, abdominal pain, vomiting, arthralgia, pyrexia, upper urinary tract infection, back pain, cough, and asthenia. Hematologic adverse drug reactions include myelosuppression: thrombocytopenia, neutropenia and anemia. In comparison to 1st line patients, Grade 3/4 adverse events were more frequently observed in CML patients resistant or intolerant to prior therapy including imatinib. Other significant drug effects reported with nilotinib include modest QTc prolongation, elevations of blood glucose, bilirubin, lipase, and transaminases, which are manageable with dose interruptions and reductions.

In general, the safety profile in GIST patients was similar to that in CML patients, with the exception of a lower incidence of hematologic toxicity in GIST patients. GI related adverse events were more frequently reported as expected in this patient population. However, given that two phase III studies designed to demonstrate the superiority of nilotinib over imatinib for the treatment of patients with GIST (one study in patients who had failed prior therapy with imatinib and sunitinib and the other in newly diagnosed untreated patients) failed to meet their primary endpoints, development of nilotinib for the treatment of GIST patients has been discontinued.

2 Study rationale/purpose

Nilotinib inhibits the tyrosine kinase activities of PDGFRA and KIT and affects the viability of the GIST cell line GIST882 with similar potency as imatinib. *In vitro* data in GIST cell lines expressing different mutations of KIT indicate that nilotinib has

antiproliferative activity against certain imatinib-sensitive and -resistant forms of KIT. Moreover, studies investigating the cellular uptake of nilotinib in comparison with imatinib have revealed that nilotinib intracellular concentrations are 7- and 10-fold higher than those of imatinib in GIST882 and GIST GDG1 cell lines respectively. Preliminary data from an ongoing Phase I study [CAMN107A2103] indicate that nilotinib is well tolerated and has clinical benefit in patients with imatinib-resistant GIST who have failed other second line targeted therapies.

Further investigation of the potential efficacy of nilotinib in a larger number of GIST patients who have failed other second line therapies are ongoing in a Phase III study [CAMN107A2201]. The study includes adult patients with unresectable or metastatic GIST showing progression of disease on both imatinib and sunitinib, or demonstrating intolerance to imatinib and/or sunitinib. In this multi-national trial a total of 44 patients from approximately 5 countries were recruited.

Further investigation of the potential efficacy of nilotinib in an earlier stage of the disease with a potential overall benefit for GIST patients is indicated based upon the experimental data indicating that nilotinib inhibits the proliferation of imatinib-resistant GIST cell lines, evidence that nilotinib is well tolerated and has clinical benefit in GIST patients.

Data from Phase II and Phase III clinical trials investigating the relationship between KIT and PDGFR mutations and response to imatinib have indicated that GISTs with different kinase genotypes differ in their clinical response. In particular, higher response rates and longer TTP have been observed for GISTs carrying KIT exon 11 mutation (Heinrich 2005, Blanke 2006). There are not such data with nilotinib and efforts will be made to perform KIT/PDGFR mutational analysis in tumor samples as part of the proposed study.

In the current trial we propose to investigate nilotinib in patients with a first line treatment. The promising efficacy data [CAMN107A2103] in combination with the safety profile of nilotinib which is comparable to imatinib allow to investigate the drug in the 1st line treatment of metastatic and/or unresectable GIST patients.

3 Objectives

3.1 Primary objective

- To evaluate the efficacy of Nilotinib in patients with unresectable or metastatic gastrointestinal stromal tumors. Efficacy is defined as the proportion of patients showing stable disease (SD), partial response (PR) or complete response (CR) during the first 6 months according to RECIST criteria.

3.2 Secondary objectives

- To evaluate the objective tumor response rate based on RECIST criteria (complete response (CR) and partial response PR)
- To evaluate time to overall response (PR or CR)
- To evaluate duration of response

- To evaluate progression free survival (PFS) during the first 6 months using RECIST criteria
- To evaluate overall survival (OS)
- To evaluate the safety and tolerability of Nilotinib as measured by rate and severity of adverse events

4 Study design

This is a multicenter, single-arm, phase II trial evaluating the Nilotinib in adult patients with unresectable or metastatic gastrointestinal stromal tumors.

A 6 month recruitment phase is anticipated to achieve an estimated total sample size of 40 subjects.

The individual treatment phase will last up to 6 months with monthly visits. Patients who profit from the treatment (SD, PR or CR) will be offered to continue on the study drug during a follow up phase.

On May 5, 2011, Novartis took the decision to discontinue the ongoing clinical trials with nilotinib in GIST. This decision was based on the recent decision to discontinue ENESTg1 study CAMN107G2301 “A randomized, open-label, muticenter phase III study to evaluate the efficacy and safety of nilotinib versus imatinib in adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST)” that have been recommended by the independent Data Management Committee (DMC) after the first planned interim analysis of this trial. This first interim analysis for futility as specified in the ENESTg1 protocol demonstrated that nilotinib is unlikely to demonstrate superiority to imatinib in progression free survival, the primary study endpoint. The independent DMC also reported that there were no safety issues identified in either arm of this trial.

Until now, trial enrollment of 44 patients was already completed. From those 44 patients, 5 patients are still ongoing and receive nilotinib as study medication. If required by specific health authorities (e.g. Afssaps-French Health Authority), all nilotinib patients will have to discontinue trial participation to receive imatinib according to local prescription practice. Following the decision to close-out the Novartis-Sponsored studies CAMN107G2301 and CAMN107DDE05, the enrollment of the study CAMN107DDE06 has being re-opened in order to ensure continued access to nilotinib to the patients currently in the CAMN107G2301 trial and CAMN107DDE05 trial in Germany and benefiting from the nilotinib treatment.

The CAMN107G2301 close-out plan included a nilotinib Roll-over trial with the aim to provide an option to all the patients currently benefiting from the nilotinib treatment and ensure continued access to the experimental drug. Since the German BfArM rejected the nilotinib Roll-over protocol due to limited safety reporting not in line with the

principles of pharmacovigilance within clinical trials and GCP and to inadequacy of the protocol to evaluate the safety of an IMP in agreement with the level of current scientific knowledge, two patients currently benefiting from the nilotinib treatment within the CAMN107G2301 trial in Germany will be without an alternative drug re-supply at the closure of the CAMN107G2301trial.

The CAMN107DDE05 close-out plan included the access to nilotinib for ongoing German patients until disease progression. As of today there are only two patients with metastatic GIST currently benefiting of the nilotinib treatment within the CAMN107DDE05 trial in Germany. Considering that these two patients are benefiting from nilotinib treatment and might continue receiving the experimental drug for a prolonged time, they will be moved to study CAM107DDE06 to allow the closure of study CAMN107DDE05.

Screening

At Visit 1 patients will be assessed for eligibility for study participation. Tumor measurements will be reported in the CRF and the images (original or copy) should be kept as part of the source documentation.

Patients will be advised that formal study entry cannot be fully determined until the completion of screening, when all inclusion/exclusion criteria have been finally assessed.

Patients moving from CAMN107G2301 and CAMN107DDE05 studies to CAMN107DDE06 study in Germany will be assessed for eligibility at Visit 1.

Patients from CAMN107G2301 and CAMN107DDE05 studies will start the treatment in study CAMN107DDE06 depending on the date of the last patient last visit in the previous study.

Tumor measurements assessed at baseline before starting treatment with nilotinib in studies CAMN107G2301 or CAMN107DDE05 and before starting treatment in study CAMN107DDE06 will be reported in the CRF and the images (original or copy) should be kept as part of the source documentation.

4.1 Study drug treatment

At Visit 2 (Day 1) eligible patients will start study treatment with Nilotinib 400 mg bid.

From May 5, 2011 on, patients still receiving nilotinib should be offered the opportunity to discontinue study drug prematurely to receive standard treatment with imatinib.

Patients who are receiving nilotinib and considered by the investigators to be deriving benefit have the option to remain on medication. Those patients will be treated with nilotinib until disease progression is determined by the local radiologist/oncologist (RECIST criteria), unacceptable toxicity, death, discontinuation from the study for another reason or to the end of the study.

Patients moving from CAMN107G2301 or CAMN107DDE05 studies to CAMN107DDE06 study in Germany will continue receiving nilotinib treatment at the dosage ongoing in studies CAMN107G2301 or CAMN107DDE05.

4.2 Follow-Up

Patients who finished the study after 6 months without progression have the option to remain on medication. Those patients may continue to be treated with nilotinib as foreseen by the protocol until disease progression by entering the follow-up or may discontinue trial participation to receive nilotinib according to a local transition plan. If required by specific health authorities (e.g. Afssaps-French Health Authority), all nilotinib patients will have to discontinue trial participation to receive imatinib according to local prescription practice.

Follow-up will continue until the patient has documented disease progression or starts another cancer therapy. The investigator/designee will document data till change of treatment.

Patients moving from CAMN107G2301 or CAMN107DDE05 studies to CAMN107DDE06 study will enter directly in the follow-up phase of study CAMN107DDE06. They will be treated with nilotinib until patient is no longer benefiting from the treatment, unacceptable toxicity, consent withdrawal, investigator decision or patient's death, whichever comes first.

The start of treatment date for patients included in CAMN107DDE06 study will be based on the date of the last patient last visits in CAMN107G2301 and CAM107DDE05 trials.

5 Population

The study population will consist of adult patients with unresectable or metastatic GIST showing progression of disease. In this multi-national trial a total of 44 patients from approximately 5 countries recruited.

The investigator or his/her designee must ensure that all patients who meet the following inclusion and exclusion criteria are offered enrollment in the study, with the exception of patients moving from studies CAMN107G2301 or CAMN107DDE05. Ad hoc criteria applies for these patients (Section 5.3).

5.1 Inclusion criteria

- Age ≥18 years
- Histologically confirmed diagnosis of GIST that is unresectable and/or metastatic and therefore not amenable to surgery or combined modality with curative intent prior to or at Visit 1
- At least one measurable site of disease on CT/MRI scan at Visit 1, as defined by RECIST criteria (see Post Text Suppl 3 for details) The scans should be at maximum 2 weeks old. New scans are only required as baseline scans if they are older than approx. 2 weeks.

- WHO Performance Status of 0, 1 or 2
- Patients must have the following laboratory values (≥ LLN (lower limit of normal) or corrected to within normal limits with supplements prior to the first dose of study medication.):
  1. Potassium ≥ LLN,
  2. Magnesium ≥ LLN,
  3. Phosphorus ≥ LLN,
  4. Total calcium (corrected for serum albumin) ≥ LLN
- Patients must have normal organ, electrolyte, and marrow function as defined below:
  1. Absolute Neutrophil Count (ANC) ≥ 1.5x 109/L;
  2. Platelets ≥ 100 x 109/L;
  3. ALT and AST ≤ 2.5 x upper limit of normal (ULN) or ≤ 5.0 x ULN if considered due to tumor;
  4. Alkaline phosphatase ≤ 2.5 x ULN unless considered due to tumor;
  5. Serum bilirubin ≤ 1.5 x ULN;
  6. Serum lipase and amylase ≤ 1.5 x ULN;
  7. Serum creatinine ≤ 1.5 x ULN or 24-hour creatinine clearance ≥ 50 ml/min. (calculated creatinine clearance using Cockroft formula is acceptable)
- Ability to understand and willingness to sign a written informed consent

5.2 Exclusion criteria

- Prior treatment with nilotinib
- Treatment with any cytotoxic and/or investigational cytotoxic drug ≤ 4 weeks (6 weeks for nitrosurea or mitomycin C) prior to Visit 1 with the exception of imatinib targeted therapy as an adjuvant therapy or imatinib in first line treatment for maximum of 4 weeks.
- Prior or concomitant malignancies requiring active treatment other than GIST with the exception of previous or concomitant basal cell skin cancer, previous cervical carcinoma in situ
- Impaired cardiac function at including any one of the following:
  1. LVEF < 45% or below the institutional LLN range (whichever is higher) as determined by echocardiogram at Visit 1
  2. Complete left bundle branch block
  3. Use of a ventricular paced cardiac pacemaker
  4. Congenital long QT syndrome or family history of long QT syndrome
  5. History of or presence of significant ventricular or atrial tachyarrhythmias
  6. Clinically significant resting bradycardia (< 50 beats per minute)
  7. QTc > 450 msec on screening ECG (using the QTcF formula). If QTc > 450 msec and electrolytes are not within normal ranges (electrolytes should be corrected and then the patient rescreened for QTc.

8. Right bundle branch block plus left anterior hemiblock, bifascicular block
9. Myocardial infarction within 12 months prior to Visit 1
10. Other clinically significant heart disease (e.g., unstable angina, congestive heart failure or uncontrolled hypertension,)

- Patients with severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol e.g. impairment of gastrointestinal (GI) function, or GI disease that may significantly alter the absorption of the study drugs, uncontrolled diabetes
- Use of therapeutic coumarin derivatives (i.e. warfarin, acenoucumarol, phenprocoumon)
- Use of any medications that prolong the QT interval and CYP3A4 inhibitors if the treatment cannot be either safely discontinued or switched to a different medication prior to starting study drug administration. Please see www.qtdrugs.org for a comprehensive list of agents that prolong the QT interval as well as [Post-Text Supplement 2].
- Patients who have undergone major surgery ≤ 2 weeks prior to Visit 1 or who have not recovered from side effects of such surgery
- Patients who have received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation < 2 weeks prior to Visit 1 or who have not recovered from side effects of such therapy
- A history of noncompliance to medical regimens or inability or unwillingness to return for scheduled visits
- Patients who are pregnant, breast feeding or women of childbearing potential (WOCBP). Post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential Women of reproductive potential, to include female partners of heterosexual or bisexual patients, must agree to use an effective method of contraception during the study and for up to three months following termination of the study.
- Patients unwilling or unable to comply with the protocol

5.3 Eligibility criteria for patients from studies CAMN107G2301 or CAMN107DDE05

Patients currently participating in the Novartis-sponsored studies CAMN107G2301 or CAMN107DDE05 and benefiting from the nilotinib treatment according to the investigator will be offered the possibility to continue treatment with nilotinib in study CAMN107DDE06.

They will be included in study CAMN107DDE06 if the following criteria are fulfilled:

- Patient has an histologically confirmed diagnosis of GIST that is unresectable and/or metastatic
- Patient is currently enrolled in the studies CAMN107G2301 or CAMN107DDE05 in Germany and is on treatment with nilotinib

- Patient is currently benefiting from the treatment with nilotinib, as determined by the investigator
- Patient has demonstrated compliance, as assessed by the investigator, within the CAMN107G2301 or CAMN107DDE05 protocols requirements
- Patient has willingness and ability to comply with scheduled visits, treatment plans and any other study procedures
- Written informed consent obtained prior to enrollment in the study
- 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.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 30 days of study medication. Highly effective contraception methods include:
    - 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 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 screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - Combination of any two of the following (a+b or a+c, or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception or other
        forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

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 (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or 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.

- Sexually active males unless they use a condom during intercourse while taking drug and for 30 days after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

6 Treatment

6.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by the sponsor to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). Once assigned to a patient, a patient number will not be reused. If the patient fails to be started on treatment for any reason, the reason for not being treated will be entered on the Screening Log, and the Demography CRF should also be completed. No other data will be entered into the clinical data base for screen failure patients.

Informed consent must be obtained before any study procedures are carried out; this includes any procedures to determine a patient's eligibility.

6.2 Investigational drug

6.2.1 Instructions for prescribing and taking the study drug

Nilotinib is available as a hard gelatin capsule and will be dosed on a flat scale of mg/day and not by weight or body surface area. It will be provided by Novartis as global clinical study supply or as local commercial packs and sourced in the country. It will be supplied to the investigator/hospital pharmacy as open-label medication and packed and labeled under the responsibility of Novartis Drug supply management. Nilotinib will be delivered as dose strength of 200 mg and supplied in blisters.

Medication labels or booklets, if used, will comply with the legal requirements of each country and be printed in the local language. They will supply no information about the patient. The patient number will be added to the label by the site personnel. The storage conditions for study drug will be described on the medication label or leaflet (in case of local commercial packs).

6.2.2 Study drug

Each study site will be supplied by Novartis with nilotinib in identically-appearing packaging. For global study supply, one component of the packaging has a 2-part label. Each part of this label will give the name and dose of the drug. There will also be a blank space that needs to be completed with the patient ID number. Immediately before dispensing study drug to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) containing that patient's unique patient number. For local commercial packs, name and dose of the drug, batch number and patient ID number will be noted in the respective Drug Label Form before dispensing.

6.2.3 Treatment

The dose of nilotinib will be 400 mg bid which is the current Phase II dose as established in study CAMN107A2101.

For patients moving from the CAMN107G2301 or CAMN107DDE05 studies to CAMN107DDE06 study the starting dose of nilotinib should be the current dose used while on treatment in the CAMN107G2301 or CAMN107DDE05 study.

6.3 Treatment arms

Not applicable. This is a single arm study.

6.4 Treatment assignment

This is a single arm study. Please see Section 6.1.

6.5 Treatment blinding

This is an open-label study and blinding is not applicable.

6.6 Treating the patient

General

Patients will be asked to take their daily medication doses at approximately the same time each day and to swallow the tablets/capsules whole and not chew them. Patients will also be advised to avoid grapefruit or grapefruit juice, Seville oranges, and star fruit and star fruit juice during the entire study as this can enhance and prolong their exposure to the study drugs.

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

6.6.1 Study drug administration

Patients should take nilotinib twice daily approximately 12 hours apart and it should not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for 2 hours before the dose is taken and no additional food should be consumed for at least one hour after the dose is taken.

6.6.2 Permitted study drug adjustments

For patients who are unable to tolerate the protocol-specified dosing schedule due to drug-related toxicity, certain dose adjustments are permitted in order to keep the patient on study drug. If a treatment interruption is needed and the patient is unable to resume treatment within a period of ≤ 21 days, the patient should be withdrawn from the study. Any changes in dose level must be recorded on the Dosage Administration Record CRF.

Dosing modifications

Please refer to Table 6-1 and Table 6-2 for dose reduction steps and criteria for interruption and re-initiation of nilotinib for drug-related toxicity.

Dose reduction will only be permitted for drug-related toxicity, and this will be permitted at any time throughout study.

Dose reduction guidelines for study drug-related non-hematologic toxicity

A summary of dose reduction guidelines for study drug-related non-hematologic toxicity is presented in Table 6-1. No dose reductions below 400 mg/day of nilotinib will be allowed. If a patient cannot tolerate a minimum dose of 400 mg/day of nilotinib, the patient must be discontinued from the study. Any non-hematologic toxicity must be resolved within 28 days in order to resume study drug at the reduced dose. If a non-hematologic toxicity does not resolve after 28 days of study drug interruption, the patient must be discontinued from the study.

Table 6-1 Summary of dose reduction guidelines for study drug-related non-hematologic toxicity – nilotinib

Worst toxicity NCI CTCAE grade	**During therapy**
No toxicity	Maintain dose level
	Nilotinib 400 mg BID
General non-hematologic toxicity	

Worst toxicity NCI CTCAE grade	**During therapy**
Grade 2 (persisting > 7 days with optimal supportive care)	Hold therapy and resume nilotinib at 400 mg BID after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume at next lower dose level l→ 400 mg QD. If another recurrence is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 400 mg QD. If another recurrence is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Serum creatinine	
Grade 2 > 1.5 -3.0 x ULN	Hold therapy and resume nilotinib at 400 mg BID after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume at next lower dose level l→ 400 mg QD; l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
≥ Grade 3 ≥ 3.0 x ULN	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 400 mg QD. If another recurrence is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Hepato-biliary [bilirubin, SGPT(AST), SGOT (ALT)]	Note: If hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), and no amylase and/or lipase elevations are seen, nilotinib may be continued at the same dose at the discretion of the investigator.
Grade 2	Hold therapy and resume nilotinib at 400 mg BID after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume at next lower dose level l→ 400 mg QD. If another recurrence is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.

Worst toxicity NCI CTCAE grade	**During therapy**
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 400 mg QD. If another recurrence is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Pancreatitis	(with abdominal symptoms plus amylase and/or lipase elevation)
Grade 2	Hold therapy and perform abdominal CT with contrast to exclude pancreatic pathology. If CT is positive, continue to hold therapy and repeat CT, at investigator's discretion. If CT is negative, re-start at the next lower dose level after recovery to ≤ Grade 1 l→ 400 mg QD. If another recurrence is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Elevated amylase and/or lipase without symptoms	
≥ Grade 3	Hold therapy and perform abdominal CT with contrast to exclude pancreatic pathology. If CT is positive, continue to hold therapy and repeat CT, at investigator's discretion. If CT is negative, re-start nilotinib at the next lower dose level after recovery to ≤ Grade 1 l→ 400 mg QD. If toxicity recurs without symptoms l→ continue dosing if CT negative, at investigator's discretion. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Diarrhea	Note: Anti-diarrheal medication is recommended at the first sign of loose stools or overt diarrhea. If diarrhea cannot be controlled with optimal anti-diarrheal treatments, take the following actions:
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 400 mg QD. If another recurrence is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.

Worst toxicity NCI CTCAE grade	**During therapy**
Vomiting	Note: The use of prophylactic medication for vomiting is not recommended. Antiemetic medication can be used as medically indicated or in the patient 's best interest. If nausea and vomiting cannot be controlled with optimal antiemetic treatment take the following actions:
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 400 mg QD. If another recurrence is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Skin rash	
Grade 2 Institute symptomatic therapy as appropriate. If skin rash does not resolve with optimal treatments, take the following actions:	Hold therapy and resume nilotinib at 400 mg BID after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy again until recovery to ≤ Grade 1 is seen and then resume at next lower dose level l→ 400 mg QD. If another recurrence is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
≥ Grade 3 Institute symptomatic therapy as appropriate. If skin rash does not resolve with optimal treatments, take the following actions	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 400 mg QD. If another recurrence is seen l→ discontinue If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Cardiac QTc prolongation	
QTcF > 480 msec	Hold dosing when an ECG with a QTc > 480 msec. ● notify the sponsor. ● Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. ● Concomitant medication usage must be reviewed. ● Compliance with correct dose and administration of Nilotinib must be checked. ● Perform a repeat ECG within one hour of the first QTc of > 480 msec. ● If QTcF remains > 480 msec, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 msec. Study drug may be restarted, at same dose, if reason for elevation of QTcF is identified and corrected so that QTcF returns to < 450 msec and to within 20 msec of baseline within 2 weeks. If the QTcF is repeated and is more than 20 msec greater than baseline or between 450 msec and 480 msec, the dose of study drug is to be reduced as follows: ● Nilotinib 400 mg BID: dose reduce to 400 mg QD. ECGs must be repeated 8 days (± 48 hours) after dose re-start for all patients who had therapy held due to QTcF > 480 msec. If QTcF of > 480 msec recurs, the patient is to be discontinued. The investigator should contact the sponsor regarding any questions that arise if a patient with QTc prolongation should be maintained on study.
Cardiac "other"	(such as unstable angina)

Worst toxicity NCI CTCAE grade	**During therapy**
≤ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen. L→ 400 mg QD If another recurrence is seen l→ discontinue If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Grade 4	Hold therapy and discontinue patient from study.

Dose reduction guidelines for study drug-related hematologic toxicity

A summary of dose reduction guidelines for ≥ Grade 3 study drug-related hematologic toxicity as determined by the investigator is presented in Table 6-2. No dose adjustments should be made for Grade 1 or 2 hematologic toxicity for nilotinib. Any hematologic toxicity must be resolved within 28 days in order to resume study drug at the reduced dose. If a hematologic toxicity does not resolve after 28 days of study drug interruption, the patient must be discontinued from the study.

Table 6-2 Summary of dose reduction guidelines for study drug-related related-hematologic toxicity – nilotinib

Worst toxicity NCI CTCAE grade	During therapy
No toxicity	Maintain dose level
	Nilotinib 400 mg BID
≥ Grade 3	Hold therapy and resume at 400 mg BID after recovery to ≤ Grade 1, if recovery occurs within 14 days If toxicity persists for 15-28 days or recurs, hold therapy and resume at next lower dose level after recovery to ≤ Grade 1: l→ 400 mg QD If another recurrence is seen l→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.

Guideline for dose re-escalation of nilotinib

Every attempt to re-escalate the dose of nilotinib to the previously administered dose level (i.e., dose level from which dose was reduced) should be made. This applies to either dose reductions due to hematologic or non-hematologic toxicities. The dose of nilotinib should be re-escalated if the following criteria are met at least one month after dose reduction:

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

For patients whose nilotinib dose was 800 mg (as 400 mg BID) prior to dose reduction to 400 mg QD, the dose would be increased to 800 mg (as 400 mg BID) if the above described criteria are met at least one month after dose reduction.

6.6.3 Other concomitant medications

All medications administered within 4 weeks prior to the administration of study drugs and all concomitant therapy administered during the study along with the reasons for therapy will be recorded in the CRF. All prior chemotherapy and biologic, immunologic, targeted therapy or radiation therapy, and surgery will be recorded on a separate page of the CRF.

- Routine prophylactic use of recombinant growth factors is prohibited while the patient is on study American Society of Clinical Oncology guidelines (Ozer 2000). However the use of growth factors is permitted at the discretion of the investigator for patients with neutropenia (ANC <500x 10^9/L). Patients who were receiving recombinant erythropoietin prior to starting study drug may continue to receive their pre-treatment doses throughout the study. If recombinant erythropoietin is required for the first time while the patient is on study, (Rizzo et al 2002) its use is permitted.
- Prophylactic anti-emetics should not be given. However when a patient has signs/symptoms of nausea and vomiting please follow directions as per Tables 6-1 and Table 6-2.
- QT prolonging agents. **Every effort should be made NOT to administer a QT prolonging agent**. If during the course of the study, concomitant administration of an agent known to prolong the QT interval is required and cannot be switched to an alternative therapy, nilotinib must be STOPPED. Please see www.qtdrugs.org for a comprehensive list of agents that prolong the QT interval as well as Post-text Supplement 2. During the course of the study if administration of a QT prolonging agent or a CYP3A4 inhibitor cannot be avoided , the Sponsor needs to be informed and it is strongly recommended that an ECG be obtained 24 to 48 hours and one week after initiating the concomitant therapy.
- In addition to medications that can affect the QT interval (Exclusion Criteria), patients must be counseled not to consume grapefruit, grapefruit juice, Seville oranges, star fruit or star fruit juice.
- CYP3A4 inhibitors. **Every effort should be made NOT to administer strong CYP3A4 inhibitors** (e.g, erythromycin, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir, mibefradil**)**. If administration of a CYP3A4 inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy, **nilotinib must be STOPPED**
  A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors and inducers may also be found at https://drug-interactions.medicine.iu.edu and Post-text Supplement 4. FDA classification of CYP3A4 inhibitors can be found at https://www.fda.gov/cder/drug/drugInteractions/tableSubstrates.htm#classInhibit. Patients must be carefully monitored for potentiation of toxicity due to individual concomitant medication.

- CYP3A4 inducers. Inducers of CYP3A4 could increase the metabolism of nilotinib and thereby decrease serum concentrations. The concomitant administration of medications that induce CYP3A4 (e.g., phenytoin, rifampin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to nilotinib. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be considered. **Every effort should be made NOT to administer strong CYP3A4 inducers** (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St John's Wort) **however, if** administration of a CYP3A4 inducer cannot be avoided during the study, temporary discontinuation of study drug is NOT required.
  Please see https://drug-interactions.medicine.iu.edu and Post-text Supplement 4 for a list of CYP3A4 inducers.
- Patients taking medications chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The days of full pharmacokinetic blood sampling should be representative of the other study days with regard to the use of chronically administered concomitant medications. However, if a concomitant medication is used intermittently during the study, this medication should be avoided on the days of full pharmacokinetic sampling, if medically feasible.
- In *in vitro* assays, nilotinib has been shown to interact with CYP 2C9, CYP 2C8, CYP 2D6 and CYP 3A4. Because of the inherent risk of either reduced activity or enhanced toxicity of the concomitant medication and/or nilotinib, medications known to interact with these cytochrome P450 isoenzymes should be used with caution (Post-text Supplement 4). Patients using concomitant medications known to be metabolized by these isoenzymes will not be excluded from the study (except for coumarin derivatives and CYP3A4 inhibitors and inducers that are contraindicated); but, the patients must be carefully monitored for potential of toxicity due to individual concomitant medications.

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

6.6.4 End of treatment and study drug discontinuation

End of treatment

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients should be withdrawn from the study if pregnancy occurs.

In addition to these requirements for study drug discontinuation, the investigator should discontinue study drug for a given patient if, on balance, he thinks that continuation would be detrimental to the patient's well-being.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment CRF. Patients may be withdrawn from the study prematurely for one of the following reasons:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- New cancer therapy
- Disease progression

Study drug discontinuation

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for that patient.

Patients who discontinue study drug before completing the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit should be performed. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 28 days following the last dose of study drug.

Patients who discontinue study drug 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. The last date of study drug intake should be entered into the Study Completion CRF and the reason for discontinuing study drug should be given on the comments page. If a patient who discontinued study drug performed all scheduled study procedures and measurements, he will be counted as a study completer.

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

Treatment after study drug discontinuation is at the discretion of the investigator.

Study evaluation completion

Survival information will be collected on all study patients until 28 day safety follow up.

7 Visit schedule and assessments

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

entered into the database (D) or remain in source documents only (S). Assessments that generate data for database entry and which are recorded on CRFs are listed using the CRF name. The screening period can be less than 14 days provided all assessments are completed. All other study visits may be scheduled allowing for ± 4 days. If any visit falls outside the ± 4 day window during the active treatment period, the patient must be seen as soon as possible and subsequent visits should be scheduled in keeping with Visit 2. Please pay special attention to drug supply needs if the visit is not scheduled as outlined in the visit schedule table (Table 7-1).

Patients moving from [CAMN107G2301] or [CAMN107DDE05] studies to [CAMN107DDE06] study will directly enter the follow up phase of the study after the screening visit. The first FU visit will be 3 months after the screening visit.

The start of treatment date for patients included in [CAMN107DDE06] study will be based on the date of the last patient last visits in studies [CAMN107G2301] and [CAM107DDE05].

Table 7-1 Visit evaluation schedule

	Baseline Screening	**Core study**								**Follow up[5] / EoT[9]**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOS**	**1 - X**
Day		**1**								
Week			**4**	**8**	**12**	**16**	**20**	**24**		**36 - X**
Demographics	X									
Written Informed Consent	X									
In-/exclusion criteria	X[6]									
Ad hoc criteria for patients moving from studies [CAMN107G2301] or [CAMN107DDE05]	X[7]									
pregnancy test	X									
relevant medical history/ current medical conditions including GIST specific history[1]	X									
Prior/ Significant non-drug therapies	X									
prior adjuvant antineoplastic treatment	X									
vital signs	X	X	x	X	X	X	X	X	X	X
height	X									
Weight	X	X	X	X	X	X	X	X	X	X
ECG	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	X[4]
physical examination	X	X	X	X	X	X	X	X	X	X
ECOG PS	X	X	X	X	X	X	X	X	X	X
hematology[2]	X	X	X	X	X	X	X	X	X	X
biochemistry[2]	X	X	X	X	X	X	X	X	X	X
Urine analysis[2]	X	X	X	X	X	X	X	X	X	X
CT / MRI	X[8]			X		X		X	X	X
tumor evaluation (RECIST)	X[8]				X			X	X	X
study drug administration	X[7]	X	X	X	X	X	X	X	X	X[3]
Adverse events	X	Ongoing data capture								Ongoing data capture
Paraffin bloc available	X[6]									

	Baseline Screening	**Core study**								**Follow up[5] / EoT[9]**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOS**	**1 - X**
Day		**1**								
Week			**4**	**8**	**12**	**16**	**20**	**24**		**36 - X**
concomitant medication	X	Ongoing data capture								Ongoing data capture
Comments		Ongoing data capture								Ongoing data capture

[1] History to include site of primary tumor, metastatic sites, GIST histology, time of relapses [redacted] tumor Kit expression[2] Please refer to Section 7.5.5 for individual hematology and biochemistry tests; a -4 day visit window is permitted
[3] No study drug administration at the end of treatment visit (EoT)
[4] Only in patients with prolongation of QTc-interval or suspect for prolongation of QTc-interval
[5] During the follow up period patients will continue to be followed every 6 months until progression . For patients moving from studies CAMN107G2301 or CAMN107DDE05 the first FU visit will be 3 months after the screening visit.
[6] Not applicable for patients moving from studies CAMN107G2301 or CAMN107DDE05
[7] Only for patients moving from studies CAMN107G2301 or CAMN107DDE05
[8] Only if CT/MRI scan was not performed within 3 months from screening visit for patients moving from studies CAMN107G2301 or CAMN107DDE05
[9] All patients will be followed for safety for 28 days following the last dose of study medication.

7.1 Information to be collected on screening failures

All patients who sign Informed Consent but who do not meet the Inclusion and Exclusion criteria at Visit 1 will only have the Screening Log pages and Demography section of the CRF completed.

7.2 Patient demographics/other baseline characteristics

Standard demographic information and medical history will be collected.

7.3 Treatments

All concomitant medication, including over-the-counter medications, taken during the course of the study must be recorded on the Concomitant Medications/Significant Non-Drug Therapies CRF.

Study drug compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information on the Drug Dose CRF page. Pill count should be captured in the Drug Compliance CRF page at each visit.

7.4 Efficacy

The following efficacy assessments will be carried out:

Tumor Evaluation with CT or MRI

Tumor evaluation, (chest, abdomen and pelvis), will be assessed at baseline by means of CT or MRI. CT scan is the preferred modality and should be used wherever possible. If the baseline chest CT shows the presence of disease it should be repeated in all subsequent exams. Measurable lesions i.e. target lesions and the non-target lesions by which subsequent response assessments will be judged must be identified during tumor assessment at baseline; the disease must be staged and progression confirmed at this time.

The CT/MRI (abdomen and pelvis) is to be repeated at week 8, week 16, week 24 and EOS. During the Follow up, the patients will have images according to the visit schedule (see Table 7-1).

All images will be read locally at the site and this interpretation will be used for all clinical decisions.

The evaluation of the primary endpoints will be done with local radiologist interpretations collected by the investigator in the CRF.

Methods used for tumor measurement

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. CT and MRI should be performed

with contiguous cuts of 7 mm or less in slice thickness. CT should be performed using a 5 mm or less contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen and pelvis.

RECIST criteria will be used for clinical decision.

7.5 Safety

7.5.1 Adverse events

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

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, **or** grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected in the End of Treatment or Survival Information CRF page. Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment.

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

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

1. The CTCAE grade 1-4
2. Its relationship to each study drug (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant

medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)

5. Whether it is serious, where a serious adverse event (SAE) is defined as one which:
   - Is fatal or life-threatening
   - Results in persistent or significant disability/incapacity
   - Constitutes a congenital anomaly/birth defect
   - Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
     - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
     - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
     - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
     - Social reasons and respite care in the absence of any deterioration in the patient's general condition
   - Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

7.5.1.1 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed until resolution or stabilization of the event. As previously stated, dose delay of ≥ 21 days require the patient to be

discontinued from the study. However, the patient will continue to be followed for toxicity as previously described. All patients will be followed for safety for 28 days following the last dose of study medication.

7.5.2 Physical examination, weight, height

A complete physical examination will be performed by the investigator at all visits. Information about the physical examination findings will be present in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included on the Relevant Medical History/Current Medical Conditions pages of the CRF. Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event part in the CRF.

7.5.3 Vital signs

At each visit (Visit 1 thru FUs) the sitting pulse rate will be measured just prior to blood pressure measurements. Blood pressure should be measured after at least 3 minutes in the sitting position. In addition, temperature and weight will be recorded; height will be measured at baseline only, Visit 1.

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

7.5.4 Performance status

WHO Performance Status Scale will be used (see Post-text Supplement 1) to assess performance at screening Visit 1 (Day -14) and will be measured at each visit, from Day 1 thru FUs.

7.5.5 Laboratory evaluations

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

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

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g. require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the appropriate comment CRF page. When abnormal laboratory values or test results constitute an adverse event (i.e., induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events CRF.

The following assessments are to be performed:

7.5.5.1 Hematology

Hemoglobin, platelets, total white blood cell count (WBC) & differential. (Visit 1 screening and Visit 2 thru FUs

7.5.5.2 Biochemistry

Sodium, potassium, chloride, bicarbonate, creatinine, glucose, blood urea nitrogen – BUN (or urea), albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin with fractionation into direct and indirect, alkaline phosphatase, lipase, amylase, calcium, magnesium, phosphorus (Visit 1 screening and Visit 2 thru FUs).

Prior to starting study medication serum potassium and magnesium levels must be within normal limits. Serum potassium and magnesium levels should to be maintained within normal limits throughout the study.

7.5.5.3 Urinalysis

Standard dipstick assessment (pH, protein, glucose, blood, ketones, nitrites, and leukocytes) (Visit 1 screening) and if any potential relevant abnormalities this must be substantiated with laboratory quantification.

7.5.5.4 Pregnancy test

Serum pregnancy test Visit 1 only for women with child bearing potential.

7.5.6 Cardiac assessments

7.5.6.1 Electrocardiogram (ECG)

Visit 1 (Day -14) all patients will have a single screening electrocardiogram (ECG). As per protocol visit schedule; at EOS ECG monitoring will be performed in all patients.

All patients with a prolongation of QTc-interval or suspect for prolongation of QTc-interval should be monitored closely at each visit with a ECG. Suspected patients are for example those with a congential prolongation of the QT-interval, patients with a significant uncontrolled heartdisaese or patients taking medication which can induce QT-prolongation such as anti-arrythmica.

7.5.7 Tumor characterizations

Pathological review

Archival tumor collection is a mandatory requirement of the study. All archival tumor from the initial diagnosis and at the time of documented disease progression prior to enrollment in this study should be collected. The pathological review will be performed on paraffin blocs. The review will be performed at the [redacted], by [redacted].

Archival tumor will not be collected for patients moving from studies [CAMN107G2301] or [CAMN107DDE05] to study [CAMN107DDE06].

[redacted]

Collection and handling of tumor paraffin blocks

Paraffin-embedded tumor samples will be collected independently of the study before and during the study from each subject for analysis that may include immunohistochemistry (IHC). No additional invasive procedure for collection of tumor samples is intended as a part of this study. The investigational sites will be responsible for gathering any paraffin blocks collected before and during this study and shipping them to the reference center. A copy of the corresponding pathology report should be sent together with the sample. Both the block and pathology report should be labeled with the study subject number, site number, and study number. The institutional medical record number and name of subject should be removed without obscuring the specimen number, summary of section information, biopsy date or relevant block annotation from the blocks or pathology report. The samples should be stored and shipped at ambient temperature every month to the reference center.

8 Safety monitoring

8.1 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after signing the informed consent and until 4 weeks after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 4-week period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE

Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Integrated Medical Safety Department.

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

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

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Integrated Medical Safety Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported.

8.2 Pregnancies

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

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

8.3 Data Monitoring Board

Not applicable

9 Data review and data management

9.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs 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 CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs, which will be documented as being the source data. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

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

9.2 Data collection

Designated investigator staff must enter the information required by the protocol onto the Novartis CRFs that are printed on 3-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to Data Management by field monitors, one copy being retained at the investigational site. Once the CRFs are received by Data Management, their receipt is recorded and they are reviewed prior to data entry.

9.3 Database management and quality control

Data from the CRFs are entered into the study database by Contract Research Organization staff following their own internal standard operating procedures that have been reviewed and approved by Novartis. Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors are corrected by Data

Management personnel. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent to Novartis so the resolutions can be entered into the database. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

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

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint agreement between the Trial Statistician and Statistical Reporting and the Clinical Trial Leader.

10 Statistical methods and data analysis

Primary efficacy and safety analyses will be conducted on all patient data at the time all patients who are still receiving study drug will have completed at least 6 months of treatment (or discontinued prematurely). The additional data for any patients continuing to receive study drug past this time, as allowed by the protocol, will be further summarized in a report once these patients completed the study.

The data from each center are intended to be pooled with data from other centers conducted under this protocol so that an adequate number of patients will be available for analysis. All statistical analyses will be performed by or under supervision of Novartis Pharma, Nuremberg, Germany. The protocol does not envisage data analyses carried out independently by the investigator; if performed, they should be submitted to Novartis before publication or presentation.

Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements. The populations, variables, and methods for analysis will be selected for their relevance for testing the hypotheses of the study and are described in more detail below.

10.1 Populations for analysis

The **intent-to-treat** (**ITT) population** will consist of all patients who received at least one dose of study drug and have at least one post-baseline assessment of the primary efficacy variable (assessment according to RECIST). Patients without any post-baseline assessment of tumor will be included if they are defined as progressive disease based on clinical evaluation.

The **per-protocol (PP) population** consists of all patients of the intent-to-treat population who show no major protocol violations. The per-protocol population will be identified before database lock.

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

Patients from the studies [CAMN107G2301] or [CAMN107DDE05], who skip the core study phase and enter directly into the follow up, will be included in the safety population only as they will not contribute to efficacy.

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

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized for the ITT population. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, minimum, median, and maximum will be presented.

Medical history will be coded using MedDRA and will be presented by system organ class, MedDRA preferred term and treatment group. Separate tables will be provided for past medical condition and current medical condition.

10.3 Treatments (study drug, concomitant therapies, compliance)

Duration (days) of application of study medication will be summarized descriptively. Dosage averages will be calculated including and excluding zero doses for periods of temporary interruption of treatment regardless of whether this was due to safety reasons or patients' non-compliance. Daily dose levels will be summarized descriptively. Frequency of dose reduction (including temporary dose interruption) for safety reasons as per protocol guidelines as well as average daily dose will be presented by visit. Reasons for dose adjustments (including temporary dose interruption) will be presented by frequency distribution. Permanent treatment discontinuations will be analyzed by frequencies. These analyses will be performed for the ITT population.

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

10.4 Primary objective

10.4.1 Variable

The primary variable is defined as the best response at month 6 determined according to the RECIST criteria (see Post-text supplement 3: Response Evaluation Criteria in Solid Tumors (RECIST)) based on local radiological assessments.

10.4.2 Statistical hypothesis, model, and method of analysis

The proportion of patients in whom a CR, PR or SD was observed will be presented with the two-sided exact 80% confidence interval (Clopper-Pearson method) for the ITT population. The absolute number of patients showing SD, PR or CR as well as the lower limit of the confidence interval for the proportion will be used to conclude preliminary activity or non-activity of the study drugs in this patient population according to the rule outlined in Section 10.6.

10.4.3 Handling of missing values/censoring/discontinuations

If progression has not been documented and one or more (non-)target lesions have not been assessed or have been assessed using a less sensitive method than baseline, the response status will be determined as UNK according to RECIST. Subjects with a best overall response of UNK will be included in the denominator but not counted as non-responders.

10.4.4 Supportive analyses

The proportion of patients in whom a CR, PR or SD was observed will be additionally presented with the appropriate 95% confidence interval for the per-protocol population.

10.5 Secondary objectives

10.5.1 Population and grouping for the analyses

The secondary efficacy variables will be analyzed using the ITT population. For convenience, any tests will be performed at a two-sided significance level of 5%, and appropriate two-sided 95% confidence intervals will be displayed. For all safety analyses, the safety analyzable population will be used.

10.5.2 Secondary efficacy variables and analyses

Objective response rate (ORR) is defined as the proportion of patients in whom a complete (CR) or partial (PR) response was observed according to RECIST at month 6. ORR will be presented with the two-sided exact 95% confidence interval (Clopper-Pearson method) for the ITT population.

Additionally, absolute and relative frequencies of patients in whom a clinical benefit (CR/PR/SD) was observed will be presented together with the 95% confidence interval. Absolute and relative frequencies together with their 95% confidence interval will be presented furthermore for each category (CR/PR/SD/PD/UNK).

Time to response is defined as the time from start of treatment to the first objective tumor response (PR or CR) observed. Patients who did not achieve a confirmed PR or CR will be censored at last adequate tumor assessment date when they did not progress (including deaths not due to underlying disease). Time to response will be explored graphically by presenting the Kaplan-Meier curve.

Duration of response is defined as the time from onset of response (CR/PR) to objective tumor progression or death from any cause. Patients not experiencing

progression or death will be censored with the date of their last adequate tumor assessment. Duration of response will be explored graphically by presenting the Kaplan-Meier curve.

Progression-free survival (PFS) is defined as the time from first study drug administration to objective tumor progression or death from any cause. If a patient has not had an event, PFS is censored at the date of last adequate tumor assessment. PFS will be explored graphically by presenting the Kaplan-Meier curve.

Overall survival (OS) is defined as the time from first study drug administration to death from any cause. If a patient is not known to have died, survival will be censored at date of last contact. OS will be explored graphically by presenting the Kaplan-Meier curve.

10.5.3 Safety parameters and analyses

Safety will be evaluated using assessment of adverse events and laboratory data. The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that are new or worsening based on the common toxicity criteria (CTC) grade. Other safety data (e.g. vital signs) will be considered as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

Safety data of the patients from the [CAMN107G2301] or [CAMN107DDE05] studies, who skip the core study phase and enter directly into the safety follow up, will be included in the safety analysis.

10.5.3.1 Adverse events (AE)

All adverse events recorded during the study will be summarized. Adverse events will be coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by the number and percentage of patients in each primary system organ class and preferred term. For summaries by severity (based on CTC grades) of event, the most severe occurrence for a particular preferred term will be used for a given patient. In the data listings of adverse events, the severity of an AE, whether or not an AE is study drug related, and whether or not it is a serious AE will be indicated. Deaths, all adverse events, serious adverse events, AE leading to study drug discontinuation, AE causing dose adjustment or interruption, and AE requiring additional therapy will be listed.

10.5.3.2 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using appropriate CTC. Laboratory data will be summarized by presenting summary statistics of raw data and changes from baseline values, by presenting worsening tables and shift tables using CTC grades as well as normal ranges (baseline to most extreme post-baseline value). Listings of laboratory values will be provided by laboratory test, notable values will be flagged..

10.5.3.3 Other safety data

Data from other tests (e.g., electrocardiogram or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

10.5.4 Biomarkers

[redacted] need to be looked at in correlation with clinical response and clinical outcome.

Other areas of interest include frequency of overall mutations and individual genotypes, location of mutations within the gene and its effect on its resistance profile, and mutation rate versus treatment duration.

Not applicable for patients moving from studies [CAMN107G2301] or [CAMN107DDE05].

10.6 Sample size calculation

The study follows an exact binomial single-stage design (A'Hern 2001). The study requires 39 evaluable subjects to decide whether the proportion responding, ***p***, is less than or equal to p_0 = 50% or greater than or equal to p_1 = 70%.

If the number of responses is 24 or more, the hypothesis that *p* is less than or equal to p_0 = 50% is rejected with a target error rate of 10% and an actual error rate of 10%. If the number of responses is 23 or less, the hypothesis that *p* is greater than or equal to p_1 = 70% is rejected with a target error rate of 10% and an actual error rate of 9.4%. The design was estimated using the procedure for single-stage phase II trials of NCSS Trial and PASS 2002.

Table 10-1 Design features for exact binomial single-stage design

		Targeted		Cut-Off		Actual	
p0	**p1**	**α**	**β**	**R + 1**	**N**	**α**	**β**
50%	70%	10%	10%	24	39	10%	9.4%

p_0 is the maximum response proportion of a poor drug. p_1 is the minimum response proportion of a good drug. N is the sample size. If the number of responses is greater or equal to R+1, p_0 is rejected. If the number of responses is lower or equal to R, p_1 is rejected. α is the probability of rejecting that p is lower or equal to p_0 when this is true. β is the probability of rejecting that p is greater or equal to p_1 when this is true.

10.7 Power for analysis of critical secondary variables

Not applicable

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Appendix 1: Administrative procedures

Regulatory and ethical compliance

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

Responsibilities of the investigator and IRB/IEC/REB

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

Informed consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). In cases where the subject's legally acceptable representative gives consent, the subject (e.g., minors, patients with severe dementia), should be informed about the trial to the extent compatible with the subject's understanding and if capable, the subject should assent, sign and personally date the written informed consent. The process of obtaining informed consent should be documented in the patient source documents. In emergency situations when prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol with documented favorable opinion of the IRB/IEC/REB. The subject or the subject's legally appointed representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

A proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study is provided as an attachment. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of

the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Amendments to the protocol

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

Discontinuation of the study

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

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

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

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug, the drug name and dose but no information about the patient.

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

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

Post-text supplement 1: ECOG Performance Status Scale

Criteria for Estimation of Performance Status

Grade	Scale
0	Fully active, able to carry out all pre-disease performance without restriction. (Karnofsky 100%)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work. (Karnofsky 80-90%)
2	Ambulatory and capable of all self-care, but unable to carry out work activities. Up and about more than 50% of waking hours (Karnofsky 60-70%)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 40-50%)
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair. (Karnofsky 10-30%)
5	Dead (Karnofsky 0%)

Sources:
Oken, MM et al, Am J Clin Oncol 5:649-655, 1982
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Post-text supplement 2: Medication that may prolong the QT interval

A list of drugs associated with QT prolongation and/or Torsades de Pointe is available online at www.qtdrugs.org.

Post-text supplement 3: Response Evaluation Criteria in Solid Tumors (RECIST)

RECIST criteria for evaluation of tumor response

Eligibility

Only patients with measurable disease at baseline should be included in the study:

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20mm using conventional techniques or ≥ 10mm with spiral CT scan (with minimum lesion size no less than double the slice thickness).
- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter
  < 20mm with conventional techniques or < 10mm with spiral CT scan), i.e. bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Methods of tumor measurement

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- **CT and MRI**: CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-8mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful

to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e. after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e. skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum of the longest diameter. The baseline sum of the longest diameter will be used as reference by which to characterize the objective tumor response.
- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Measurements of these lesions are not required, but the presence or absence or worsening of each should be noted throughout the study.

Evaluation of target and non-target lesions

To assess tumor response, the sum of the longest diameter for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for target (Table 11-1) and non-target lesions (Table 11-2).

These evaluations are then used to calculate the overall lesion response considering both, the target and non-target lesions together (Table 11-3).

Table 11-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.
Progressive Disease (PD):	At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of longest diameter recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameter since the treatment started.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a less sensitive method than baseline.

Table 11-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s)
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.[1]
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a less sensitive method than baseline.

Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

The response for non-target lesions is CR only if all non-target lesions which were evaluated at baseline are now all absent. If any of the non-target lesions is still present, the response can only be 'Incomplete response/Stable disease' unless any of the lesions was not assessed (in which case response is UNK) or worsened (in which case response is PD).

Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 11-3.

Table 11-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Incomplete response/SD	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1] This overall lesion response also applies when there are no non-target lesions at baseline
[2] Once confirmed PR was achieved, all these assessments are considered PR.

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least one SD assessment > 6 weeks after start of treatment (and not qualifying for CR or PR).
- PD = progression or death due to underlying cancer ≤ 12 weeks after start of treatment (and not qualifying for CR, PR or SD). Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is available and patient discontinued due to 'Disease progression'.
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status, e.g. PR or SD, as this would imply that one or more lesions reappeared, in which case the status would become a PD.

Overall lesion responses of PR must stay the same or improve over time until progression sets in, with the exception of a UNK status. However, if a patient has a PR (≥ 30% reduction of tumor burden compared to baseline) at one assessment, followed by a < 30% reduction from baseline at the next assessment (but not > 20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented.

If the patient progressed but continues study medication, further assessments are not considered for the determination of best overall response.

The best overall response for each patient will be determined based on investigator assessments (‘Investigator best overall lesion response’).

Post-text supplement 4: Substrates of cytochrom P450 isoenzym

Patients should be instructed not to take grapefruit, St John's Wort or Seville (sour) orange juice while receiving study treatment throughout the study due to potential CYP3A4 induction or inhibition.

A list of drugs that are inducers and inhibitors of CYP3A4 is provided at https://drug-interactions.medicine.iu.edu.

Table 11-4 Medications that can induce CYP3A4

Category	Drug Names
Strong inducers of CYP3A4[1]	avasimibe, carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John's wort (*Hypericum perforatum*)[4]
Moderate inducers of CYP3A4[2]	bosentan, dabrafenib, efavirenz, etravirine, genistein[5], lersivirine , lopinavir, modafinil, nafcillin,semagacestat, talviraline, telotristat, thioridazine, tipranavir/ritonavir
Weak inducers of CYP3A4[3]	amprenavir, aprepitant, armodafinil, artesunate/ mefloquine, bexarotene, boceprevir, brivacetam, clobazam, danshen (*Salvia miltiorrhiza*)[4], dexamethasone, echinacea (*Echinacea purpurea*)[1], elvitegravir-cobicistat-emtricitabine-tenofovir (Stribild), eslicarbazepine, ginkgo (*Ginkgo biloba*)[4], ginseng[4], glycyrrhizin[5], isavuconazole, lesinurad, methylprednisolone, nevirapine, ombitasvir/ paritaprevir/ dasabuvir/ritonavir (Viekira Pak), oritavancin, oxcarbazepine, pioglitazone, pleconaril, prednisone, pretomanib, primidone, quercetin[5], raltegravir, ritonavir, rufinamide, sarilumab, sirukumab, sorafenib, sulfinpyrazone, telaprevir, terbinafine, ticagrelor, ticlopidine, topiramate, troglitazone, vemurafenib, vicriviroc/ritonavir, vinblastine, yin zhi huang[4]

[1] 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%.

[2] 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%.

[3] A weak inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 20-50%.

[4] Herbal product

[5] Food product

This list was based on information from the FDA's "Guidance for Industry, Drug Interaction Studies", from the Indiana University School of Medicine's "Clinically Relevant" Table, from the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated January 2018) for update or more details.

Table 11-5 Medications that can inhibit CYP3A4

Category	Drug Names
Strong inhibitors of CYP3A4[1]	atazanavir/ritonavir[7], boceprevir, cobicistat, conivaptan, clarithromycin, danoprevir/ritonavir[7], darunavir/ ritonavir[7], elvitegravir/ritonavir[7], grapefruit juice[6], idelalisib, indinavir, indinavir/ ritonavir[7], itraconazole, ketoconazole, lopinavir /ritonavir[7], mibefradil, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[7], posaconazole, ritonavir, saquinavir/ ritonavir[7], saquinavir, telaprevir, telithromycin, tipranavir/ritonavir[7], troleandomycin, voriconazol
Moderate inhibitors of CYP3A4[2]	aprepitant, amprenavir, asafoetida resin (Ferula asafoetida)[4], atazanavir, cimetidine, casopitant, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, grapefruit juice[6], imatinib, isavuconazole, netupitant, nilotinib, Schisandra sphenanthera (nan wu wei zi)[4], tofisopam, verapamil
Weak inhibitors of CYP3A4[3]	almorexant, alprazolam, amiodarone, amlodipine, atorvastatin, azithromycin, berberine[4], bicalutamide, blueberry juice[8], brodalumab, chlorzoxazone, cilostazol, clotrimazole, cranberry juice[8], daclatasvir, delavirdine, evacetrapib, everolimus, flibanserin, fluvoxamine, fosaprepitant (IV), fostamatinib, garden cress seeds (Lepidium sativum)[5], ginkgo (Ginkgo biloba)[4], goldenseal (Hydrastis canadensis)[4], grazoprevir, guan mai ning[4], isoniazid, ivacaftor, lacidipine, linagliptin, lomitapide, obeticholic acid, oral contraceptives, palbociclib, pazopanib, peppermint oil[5], piperine[5], pomelo (Citrus grandis)[5], propiverine, ranitidine, ranolazine, resveratrol[4], roxithromycin, Seville orange juice[5], simeprevir, sitaxentan, suvorexant, tabimorelin, tacrolimus, teriflunomide, ticagrelor, tolvaptan, tong xin luo[4]

[1] 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.

[2] 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.

[3] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-foldbut equal to or more than 1.25-fold.

[4] Herbal product

[5] Food product

[6] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent.

Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

[7] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database.

[8] The effect of certain fruit juices varies widely among brands and is concentration-, dose-, and preparation dependent.

This list is based on information 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. Please note that this is not an exhaustive list. Please refer to footnotes. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated January 2018) for update or more details.

Table 11-6 CYP3A4 substrates: Narrow therapeutic index, sensitive, and others

Category	Drug Names
Narrow Therapeutic index substrates of CYP3A4[1]	alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfanadine, thioridazine
Sensitive substrates of CYP3A4[2]	alfentanil, alpha-dihydroergocryptine, almorexant, alisoporivir, aplaviroc, aprepitant, atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, cobimetinib, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutinib, indinavir, isavuconazole, ivabradine, ivacaftor, levomethadyl (LAAM), lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, paritaprevir, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, tacrolimus, terfenadine, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
Other Substrates of CYP3A4[3]	alprazolam, ambrisentan, amlodipine, antipyrine, aripiprazole, artemether, avosentan, boceprevir, bosentan, buprenorphine, Cannabis sativa[4], carbamazepine, dexloxiglumide, dextromethorphan, diazepam, docetaxel, enzalutamide,

	gemigliptin, halofantrine, imipramine, lansoprazole, lidocaine, linagliptin, loperamide, loratadine, losartan, lurasidone, macitentan, methadone, mirodenafil, montelukast, morphine, nelfinavir, netupitant, nevirapine, nifedipine, nilotinib, nitrendipine, omeprazole, ospemifene, oxycodone, paclitaxel, pazopanib, pioglitazone, quinine, ranolazine, repaglinide, rifabutin, ritonavir, roflumilast, saxagliptin, selegiline, sertraline, sibutramine, sotrastaurin, telaprevir, theophylline, tirilazad, tolterodine, udenafil, vincristine, voriconazole
[1] Narrow therapeutic index substrates are drugs whose exposure-response relationship indicates that increases in their exposure levels by the concomitant use of an inhibitor may lead to serious safety concerns or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood (thus safe and effective use requires careful dosage titration and patient monitoring). [2] Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. [3] Other substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. [4] Tetrahydrocannabinol (∆9THC) and cannabidiol (CBD) are major constituents. ∆9THC is primarily metabolized by CYP2C9 to an active metabolite 11-hydroxy-∆9-THC (11-OH-THC). CBD is extensively metabolized by CYP2C19 and CYP3A4 to eight monohydroxylated metabolites. The effects of multiple daily doses of rifampicin 600 mg for 10 days, ketoconazole 400 mg for 6 days and omeprazole 40 mg for 6 days on the PK of ∆9THC, 11-OH-THC and CBD after a single dose (4 sprays) of an oromucosal spray were determined in a randomized, crossover, parallel study in three groups of 12 male subjects. Ketoconazole increased the Cmax and AUC0-24 of ∆9THC by 1.2- and 1.8-fold, respectively, increased the Cmax and AUC0-24 of 11-OH-THC by 3.0- and 2.6-fold, respectively, and increased the Cmax and AUC0-24 of CBD by 2- and 2-fold, respectively. Rifampicin decreased the Cmax and AUC24 of ∆9THC by 40 and 20%, respectively, decreased the Cmax and AUC0-24 of 11-OH-THC by 85 and 87%, respectively, and decreased the Cmax and AUC24 of CBD by 50 and 60%, respectively. There were no effects of omeprazole on the plasma concentrations of all three cannabis constituents.	

This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated January 2018) for update or more details.