**SUPPLEMENTARY METHODS**

**Eligibility criteria**

1. Inclusion Criteria

1.1. At least 18 years of age at the time of study entry.

1.2. Histologically confirmed metastatic and/or unresectable GIST. Patients must demonstrate prior failure to at least imatinib, sunitinib and regorafenib (4th line and beyond). Any number of previous therapies for GIST is allowed.

Failure of imatinib is defined as either prior progression of disease on imatinib in the metastatic setting or progression during adjuvant imatinib, or within 3 months of completing adjuvant imatinib. Failure of sunitinib and regorafenib is defined only as prior progression of disease on sunitinib or on regorafenib as assessed by the investigator.

1.3. Measurable disease per modified RECIST 1.1. A lesion in a previously irradiated area is ineligible to be considered as measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment.

1.4. ECOG performance status 0 or 1 (see Appendix A).

1.5. Participants must have adequate organ and marrow function as defined below (within 7 days prior to enrollment):

a. Hemoglobin ≥ 9.0 g/dL (90 g/L). Previous transfusion is allowed.

b. Absolute neutrophil count ≥ 1500/mm3.

c. Platelets ≥ 100,000 /mm3. Previous transfusion is allowed.

d. International normalized ratio (INR), and prothrombin time (PT) ≤1.5 x ULN (patients who are being prophylactically anticoagulated with an agent such as coumadin or low molecular weight heparin (LMWH) or therapeutically anticoagulated with LMWH will be allowed to participate provided they are stable and monitored at appropriate intervals per institutional guidelines throughout study).

e. Alanine aminotransferanse (ALT) and aspartate aminotransferanse (AST) ≤ 2.5 x upper limit of normal (ULN), or ≤ 5.0 x ULN if liver metastases are present.

f. Alkaline phosphatase (ALP) limit < 2.5 x ULN or ≤ 5.0 x ULN if liver metastases are present.

g. Total serum bilirubin ≤ 1.5 x ULN. Patients with Gilbert’s syndrome with baseline serum bilirubin exceeding this limit are allowed to participate.

h. Serum sodium within normal limits.

i. Glomerular filtration rate (GFR) ≥ 30 ml/min/1.73 m2 according to the MDRD (modified diet in renal disease) abbreviated formula (see Appendix B).

j. Serum phosphate levels ≥ 2.5 mg/dL or ≥ 0.8 mmol/L.

1.6. Patients must be able to swallow oral medication.

1.7. Willingness to use effective means of birth control throughout the duration of clinical study and for at least 3 months after completion of study drug.

1.8. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of study drug administration.

1.9. Ability to understand and the willingness to sign a written informed consent document.

2. Exclusion Criteria

2.1. Use of any approved tyrosine kinase inhibitors or investigational agents within 2 weeks or 6 half-lives of the agent, whichever is shorter, prior to receiving study drugs.

2.2. Patients with intolerance to sunitinib and/or regorafenib.

2.3. Participants who have had radiotherapy within 4 weeks prior to study entry.

2.4. Major surgery, or significant traumatic injury within 4 weeks prior to study entry.

2.5. Presence of symptomatic or uncontrolled brain or central nervous system metastases.

2.6. Known or suspected allergy to the investigational agent or any agent given in association with this trial.

2.7. Individuals with a history of a different malignancy, other than cervical cancer in situ, basal cell or squamous cell carcinoma of the skin, are ineligible, except if they have been disease-free for at least 5 years, and are deemed by the investigator to be at low risk for recurrence of that malignancy OR other primary malignancy is neither currently clinically significant nor requiring active intervention.

2.8. Clinically significant cardiac arrhythmias and/or patients who require anti-arrhythmic therapy (excluding beta blockers or digoxin). Patients with controlled atrial fibrillation are not exluded.

2.9. History of clinically significant cardiac disease or congestive heart failure > NYHA class 2. Patients must not have unstable angina (anginal symptoms at rest) or new-onset angina within the last 3 months or myocardial infarction within the past 6 months.

2.10. Hypertension as defined by systolic blood pressure >140 mmHg or diastolic blood pressure > 90 mmH despite optimal medical management.

2.11. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within the 6 months before start of study medication (except for adequately treated catheter-related venous thrombosis occurring more than 1 month before the start of study medication).

2.12. Patients with evidence or history of any bleeding diathesis, irrespective of severity.

2.13. Ongoing infection > Grade 2.

2.14. Patients with any seizure disorder requiring medication.

2.15. Non-healing wound, ulcer, or bone fracture.

2.16. Persistent proteinuria Grade 2 or higher measured by urine protein:creatinine ratio on a urine sample or during 24-hour assessment.

2.17. HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with sunitinib and regorafenib.

2.18. Patients with active hepatitis B or C, or chronic hepatitis B or C requiring treatment with antiviral therapy, because of potential risk of lethal liver toxicity.

2.19. Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.

2.20. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, clinically significant cardiac and pulmonary disease; liver diseases such as cirrhosis, chronic active or persistent hepatitis; or acute/ chronic medical/ psychiatric illness/ social situations or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or limit compliance with study requirements, or interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study.

2.21. Pregnant or lactating females.

2.22. Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

2.23. Strong CYP3A4 inhibitors (e.g. clarithromycin, indinavir, itraconazole, ketoconazole , nefazodone , nelfinavir , posaconazole, ritonavir, saquinavir, telithromycin, voriconazole) or strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampin, St. John’s Wort) within 28 days or 5 drug half-lives (if drug half-life in patients is known), whichever is longer, before start of study treatment.

**Definition of dose-limiting toxicity**

Dose-limiting toxicities (DLTs) during cycle 1 (28 days) were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 4.03 as grade 3–4 non-hematologic adverse events (AE), or hematologic toxicity defined as grade 3-4 febrile neutropenia, grade 4 neutropenia lasting ≥ 7 days, grade 4 thrombocytopenia or grade 3 thrombocytopenia complicated by hemorrhage. Treatment delay of > 1 week due to delayed recovery was considered a DLT.

**Management of toxicity**

Toxicity was evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Dose-reduction due to grade 3-4 toxicity beyond the DLT window involved one dose level reduction of both drugs, unless at investigator discretion attribution of AEs to a single drug was possible. In case of medium- to long-term grade 1-2 toxicities creating significant impairment in patient’s quality of life, one drug was reduced if a particular AE was attributed to one of both drugs, or regorafenib was reduced if a particular AE was attributed to both drugs. If toxicity did not improve to grade ≤ 1 in ≤ 7 days, it was mandatory to reduce one dose level the second drug that was not previously reduced. Treatment was not limited to a certain number of cycles and continued until disease progression, unacceptable toxicity, investigator’s decision or withdrawal of consent.

**Pharmacokinetic (PK) analysis**

Plasma concentrations of sunitinib, sunitinib metabolite SU012662, regorafenib and regorafenib pharmacologically active metabolites (M-2 and M-5) were measured in blood samples collected at pre-specified timepoints during cycle 1. Plasma concentrations of these compounds were determined using a validated liquid chromatography - tandem mass spectrometry method. [13] PK testing was performed at Wuxi AppTec Com., Ltd. Shanghai, China. PK parameters, including maximum plasma concentration, area under the plasma concentration-time curve and time to reach maximum plasma concentration were calculated using non-compartmental methods.