

A Two-Part Phase 1/2 Study to Determine Safety, Tolerability, Pharmacokinetics, and Activity of K0706, a Novel Tyrosine Kinase Inhibitor (TKI), in Healthy Subjects and in Subjects with Chronic Myeloid Leukemia (CML) or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

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| Protocol Number: | CLR_15_03 |
| IND Number: | ██████████ |
| EudraCT Number | 2016-001754-18 |
| Product: | K0706 capsules |
| Indication: | Treatment of adult subjects with chronic phase, accelerated phase, or blast phase CML or Ph+ ALL |
| Clinical Phase: | 1/2 |
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| Sponsor: | Sun Pharma Advanced Research Company (SPARC) Limited |
| Version/Amendment: | Version 12 / Amendment 12 |
| Date: | 12 Sep 2019 |

This protocol is the confidential property of SPARC and is intended solely for the guidance of this clinical investigation. This protocol may not be disclosed to parties not associated with the clinical investigation or used for any other purpose without the prior written consent of SPARC.

1 STUDY CONTACTS

PRINCIPAL/COORDINATING INVESTIGATOR (Part A):

[REDACTED]
[REDACTED] [REDACTED] [REDACTED]
[REDACTED]
[REDACTED] [REDACTED]
[REDACTED] [REDACTED]
[REDACTED] [REDACTED]

STUDY CENTER (Part A):

[REDACTED]
[REDACTED] [REDACTED] [REDACTED]
[REDACTED]
[REDACTED] [REDACTED]

COORDINATING INVESTIGATOR (Parts B and C):

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

STUDY CENTERS (Parts B and C):

Parts B and C will be conducted multi-nationally in approximately 90 study centers.

24 HOUR MEDICAL CONTACT:

Emergency medical contact numbers

[REDACTED]
[REDACTED] [REDACTED]
[REDACTED]

SPONSOR REPRESENTATIVE & MEDICAL CONTACT:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

SPONSOR:

Sun Pharma Advanced Research Company, Ltd
17-B, Mahal Industrial Estate, Mahakali Caves Road, Andheri
Mumbai 400093, India
Tel: +91 22 6645 5645
Fax: +91 22 6645 5685

BIOANALYTICAL ANALYSIS:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

LABORATORY ANALYSIS:

The details of the laboratory analysis are detailed in the Study Laboratory Manual.

PHARMACOKINETIC ANALYSIS:







































































































[REDACTED]
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3 PROTOCOL SUMMARY

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| Name of Sponsor/Company: | Sun Pharma Advanced Research Company (SPARC) Limited |
| Name of Finished Product(s): | K0706 capsules |
| Name of Active Ingredient(s): | K0706 |
| Title of Study: A Two-part Phase 1/2 Study to Determine Safety, Tolerability, Pharmacokinetics, and Activity of K0706, a Novel Tyrosine Kinase Inhibitor (TKI), in Healthy Subjects and in Subjects with Chronic Myeloid Leukemia (CML) or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL) | |
| Investigators: <u>Part A</u> Principal/Coordinating Investigator: [REDACTED] <u>Parts B and C</u> Coordinating Investigator: [REDACTED] | |
| Study Centers: <u>Part A</u> Part A of the study will be performed at multiple study centers in the United States. <u>Parts B and C</u> Parts B and C will be conducted multi-nationally at approximately 90 study centers. | |
| Clinical Phase: | 1/2 |
| Objectives: <u>Part A</u> <i>Primary Objective:</i> <ul style="list-style-type: none"> To examine the safety and tolerability of single oral doses of K0706 in healthy male subjects <i>Secondary Objective:</i> <ul style="list-style-type: none"> To characterize the pharmacokinetics (PK) of K0706 after single oral doses in healthy male subjects To characterize the PK of K0706 after single oral dose, in fasted and fed state in healthy male subjects <u>Part B</u> <i>Primary Objectives:</i> <ul style="list-style-type: none"> To determine the maximum tolerated dose (MTD; or recommended Phase 2 dose [RP2D]) of K0706 administered orally To evaluate the safety of K0706 <i>Secondary Objectives:</i> <ul style="list-style-type: none"> To evaluate the therapeutic activity of K0706 | |

- To evaluate the PK of K0706 after multiple oral doses

Exploratory Objectives:

- To evaluate the correlation of therapeutic activity of K0706 in the context of different baseline BCR-ABL mutation profiles
- To evaluate the BCR-ABL mutation profile at disease progression (should it occur) for possible mechanisms of resistance

Part C

Primary Objective:

- To evaluate the anti-leukemic efficacy of K0706 in subjects with CML-CP by cytogenetic outcomes and in subjects with CML-AP & BP by hematologic outcomes who have failed ≥ 3 TKIs, one of which includes ponatinib

Secondary Objectives: To evaluate

- Anti-leukemic efficacy of K0706 by molecular outcomes
- Anti-leukemic efficacy of K0706 by hematological outcomes in CML-CP
- Anti-leukemic efficacy of K0706 by cytogenetic outcomes in CML-AP & BP
- Time to response
- Duration of response
- Progression free survival (PFS) and Overall survival (OS)
- Population PK of K0706
- Safety of K0706

Exploratory Objectives:

- To evaluate the correlation of therapeutic activity of K0706 in the context of different baseline BCR-ABL mutation profiles
- To evaluate the BCR-ABL mutation profile at disease progression (should it occur) for possible mechanisms of resistance

Methodology:

This is a Phase 1/2 study of K0706 consisting of Parts A, B, and C

Part A

Part A of the study, Single Ascending Dose study in healthy human volunteers, is completed. For further details of the study design and the outcomes, please refer to the Appendix III (Section 13.3).

Part B

Part B of the study will be an open-label, dose-ranging, single-agent, multicenter, multidose, dose escalation study initiated in subjects with Ph+ CML (Ph + CML include CML-CP, AP and BP; [without the BCR-ABL T315I mutation until sufficient plasma levels found to be active preclinically in the T315I clone are achieved]) and Ph+ ALL. Eligible subjects will be treated in [REDACTED] cycles of once daily self-administered K0706. While K0706 should be preferably taken [REDACTED], the subjects should maintain approximately [REDACTED] K0706 dosing in all cycles.

To determine the MTD and/or the RP2D, the study will initiate with an accelerated titration dose escalation design and will transition to a 3+3 design when the first subject enrolled in the initial accelerated titration dose escalation cohort develops grade 2 or higher AE that is not clearly and incontrovertibly related to the underlying disease, co-morbidities, or concomitant medication.

The initial dose escalation cohorts can enroll at least 1 and up to 3 subjects into each cohort. The subject enrolled into each cohort following the accelerated design of the initial escalation steps will receive the initial IMP administration and continue to receive IMP at the same dose daily (unless [s]he

qualifies for intra-subject escalation as described below). In cases where more than 1 subject have been entered in the accelerated titration component of the study, only the 1st subject will be evaluable unless the Sponsor and Investigator deem otherwise. If the first subject enrolled in this cohort does not experience Grade 2 or higher AEs or DLTs during Cycle 1 of his/her study treatment (),

the dose for the next subject(s) will be escalated to the next dose level. Enrollment into subsequent cohorts will proceed only after the current cohort has completed Cycle 1 of study treatment. When more than 1 subject is enrolled, enrollment may occur concurrently.

A subject administered a dose lower than the highest studied dose may have his/her dose increased up by one dose level at a time or to a dose that is 1 dose level below the highest studied dose, as per Investigator's discretion provided that:

1. The dose cohort to which the patient is being escalated has been completed (e.g., 1 cycle has been completed for all subjects)
2. The subject has not previously experienced a DLT
3. The subject has no residual study drug-related toxicity that is greater than grade 1

Any results from intra-subject dose escalations will not affect inter-subject dose escalations unless the Investigator and Sponsor agree that intra-subject escalation information reasonably alters the potential benefit-risk ratio for subsequently treated subjects. Dose escalations should occur at the beginning of a new cycle. Safety findings from intra-subject escalations will not be used for determination of the MTD of a regimen.

If the first subject enrolled in the initial accelerated titration dose escalation experiences a Grade 2 or higher AE that is not clearly and incontrovertibly related to the underlying disease or concomitant medications in a cohort, then that cohort and all the subsequent cohorts will follow the standard 3+3 design. All toxicities will be considered while making decisions regarding drug escalation increments or discontinuations, unless they are clearly and incontrovertibly related to the underlying disease or concomitant medications.

For the cohorts where the 3+3 design applies, 3 subjects will be enrolled initially. If 2 of these subjects experience a Grade 2 or more toxicity (that is not clearly and incontrovertibly related to the underlying disease or concomitant medications), subsequent cohorts will be escalated according to smaller increments. Further, if there are no DLTs in the first 3 subjects, dose-escalation to the next higher dose level may proceed. If 1 of the 3 subjects experiences a DLT, that dose level will be expanded to 6 subjects (3 additional subjects will be enrolled). If 2 subjects at a given dose level experience a DLT, the MTD will have been exceeded. The next lower dose level will be expanded to 6 subjects, or if 6 subjects have already been enrolled and no more than 1 of the 6 subjects experienced a DLT, then this lower dose level will be considered the MTD. Additional subjects may be enrolled in dose escalation cohorts for further assessment of safety and efficacy of K0706 at doses that have been tolerated (i.e.: doses which have < 2 DLTs in 6 enrolled subjects or < 1 DLT in 3 enrolled subjects).

Once the MTD or RP2D is established, the Sponsor and Principal Investigators may elect to add up to 12 additional subjects in each of the subgroups as expansion cohorts (i.e.: CML-CP, CML-AP, CML-BP, T315I CML-CP and Ph+ ALL) using the modified toxicity probability interval design starting at the MTD or RP2D for each subset of subjects.

subjects with T315I mutations will not be enrolled in any part of the study.

Subject(s) in the subgroup expansion cohorts will start at MTD or RP2D achieved in the dose escalation cohorts. Initially, three subjects will be enrolled into each of the subgroup expansion cohort and monitored for DLTs. An internal Data Monitoring Committee (iDMC) will be convened after the 3 subjects have completed the DLT observation period. Stopping rules and subsequent dosing strategy will be made as per the algorithm described in the schematic for modified toxicity probability interval. The iDMC may recommend enrolling subsequent subjects at the same dose level if escalation criteria are met

(e.g. DLTs in $\leq 1/3$ subjects) depending on emerging safety-efficacy profile. The second set of up to 9 subjects will be enrolled if the stopping rule is not met after review of data from first 3 subjects. Separate MTD or RP2D may be identified for CML-CP, CML-AP, CML-BP, T315I CML-CP and Ph+ ALL.

RP2D will be the dose level selected for further evaluation; selection of the RP2D will be based on safety, tolerability, PD, preliminary anticancer activity findings, and the observed trough blood levels for K0706 relative to levels found to be active preclinically.

The decision to advance to the next dose level will only occur after careful evaluation of safety and tolerability data for a given dose level by the Sponsor and Principal Investigator after completion of Cycle 1; data from later cycles of treated subjects may be taken into consideration in this decision.

An IDMC consisting of members from the Sponsor, the investigative site, the CRO and an independent member will be formed to oversee the study. A formal charter will be generated that will describe the responsibilities of this group and will be submitted as an IND amendment prior to the initiation of Part B.

A subject experiencing a DLT may continue therapy [REDACTED]. Subjects who experience a DLT and recover, may be treated (at the Investigator's discretion) at the next lower dose level until disease progression or other events requiring further dose reduction exist. [REDACTED]

Further dose reduction or delay or both may be implemented basis joint discussion between investigator and sponsor's medical monitor basis evaluation of subject's clinical condition. [REDACTED]

Part B of the study will consist of a screening wherein all the required clinical and laboratory investigations to establish the eligibility of the subject for the trial are completed. Subject's disease diagnosis and status will be confirmed using the pathology reports available with the subject at the time of screening initiation. Only the latest pathology reports, subsequent to which there has been no change in therapy (with a potential to affect the disease course), will be considered for screening. [REDACTED]

[REDACTED] subjects will be reviewed on a case-by-case basis in consultation with the medical monitors of the CRO and/or Sponsor. [REDACTED]

Subjects will enter the study center [REDACTED] to receive the first administration of IMP and will complete the required assessments and sample collections ([REDACTED]).

[REDACTED]. Subjects may be admitted a day prior to Cycle 1 Day 1 dosing and if required stay overnight at the study center on Cycle 1 Day 1, based on Investigator's discretion. Subjects will complete the assessments on Cycle 1 Day 2 and may remain in the study center overnight for observation, at the discretion of the Investigator. Subjects will return for follow-up assessments ([REDACTED]) [REDACTED].

Cycle 2 will have similar [REDACTED] sample collections on Day 1, and subjects will be required to return to the study center [REDACTED] for [REDACTED] other follow-up assessments.

From Cycle 3 onwards, subjects will only be required to return to the study center once every [REDACTED]

[REDACTED] Note: The last observation/evaluations for each cycle may coincide with the Day 1 of next cycle e.g., Cycle 6 Day [REDACTED] observation may coincide with Cycle 7 Day 1). [REDACTED] samples will be collected on the day of the study visit from Cycle 3 onwards.

Subjects will remain on study treatment for approximately 60 months (i.e.: 5 years from 1st K0706 dosing), or until intolerance, subject withdraws from the study, or progression of disease. Subjects who discontinue the study will be followed up for survival (survival assessment includes information about subject survival and other anticancer therapies) every 3 months after the IMP discontinuation till 60 months from their first dose of K0706 or until death, withdrawal of consent, or the end of the study, whichever comes first.

Treatment beyond 60 months will be considered, provided the Investigator considers that the subject is benefiting from K0706 therapy. Subjects who continue to receive K0706 beyond 60 months will be followed up for safety, survival and response assessments. Information about subject's survival and disease response will be collected at the follow up visits every 3 months in these subjects.

Medical Care of Subjects after the End of Treatment Visit:

After a subject has completed the study or has withdrawn early from the study, usual treatment (as per the local standards of care) may be administered, if required, in accordance with the study center's generally accepted medical practice and depending on the subject's individual medical needs. The Sponsor will not have any role to play in further treatment and the treatment regimen followed will be outside the purview of the study protocol. Information about subject's survival and anticancer therapies will be collected every 3 months for approximately 60 months from the subject's first dose, by telephone contact, medical record review, and/or study center visits until death, withdrawal of consent, or the end of the study, whichever comes first. This information will be documented by the study center personnel in the subject's source documents and the electronic data capture system.

Part C:

Part C will be a multicenter, phase 2, single arm, open-label study of oral K0706 in subjects with Ph+ CML (CP, AP and BP) who have resistance and/or intolerance to ≥ 3 prior TKIs one of which includes ponatinib. Subjects must have documented evidence of intolerance and/or primary (never had a response) or secondary resistance (loss of a response) following standard or high dose TKI therapy (refer Inclusion Criteria # 3). Subjects with Ph+ ALL will not be included in Part C of the study.

Subjects in Part C will be grouped in the following cohorts:

| Cohort A | Cohort B | Cohort C |
|--------------------------------------|--|------------------------------------|
| Ph+ CML Chronic Phase (CP) cohort | Ph+ CML Accelerated Phase (AP) cohort | Ph+ CML Blast Phase (BP) cohort |

Note: The number of subjects contributed by a site should not exceed approximately 20% of total study population as far as possible unless approved by the Sponsor.

Entry into disease cohort will happen during screening. If there is a change in disease status (e.g. from CML-CP to CML-AP) during screening (i.e., prior to assignment to a Cohort), re-assignment to appropriate cohort is permitted. Each of the three cohorts are representative of distinct patient populations and will be evaluated separately for efficacy and safety.

Eligible subjects will be treated in [REDACTED] cycles with once-daily, oral self-administered 174 mg of K0706 and will be evaluated for K0706 anti-leukemic activity (hematological, cytogenetic and molecular response). Intra patient dose escalation is permitted only for Part C subjects enrolled at [REDACTED]. Patients enrolled in Part C at [REDACTED] can be escalated upto 174 mg based on investigator's assessment of subject's tolerability and response.

Adverse events (AEs) will be assessed throughout the study until 30 days after discontinuation of the study drug. AEs will be graded as per National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. Any AE/SAE reported by the patient after the completion of AE collection period and considered related to the study drug should also be reported by the investigator. AEs will be followed to a satisfactory resolution, until it becomes stable, or until it can be

explained by another known cause (i.e. concurrent condition or medication) and the clinical judgment of Investigator indicates that further evaluation is not warranted. Disease progression is not considered an AE in this study unless it leads to death or hospitalization in which case it should be reported as SAE.

A Data Safety Monitoring Board (DSMB) will be established for periodic review of safety data for this study.

The study will consist of screening wherein all the required clinical and laboratory investigations to establish the eligibility of the subject for the trial is completed. Subject's disease diagnosis and status will be confirmed using the pathology reports available with the subject at the time of screening initiation. Only the latest pathology reports, subsequent to which there has been no change in therapy (with a potential to affect the disease course), will be considered for screening. Pathology reports and documented intolerance on the prior TKIs received by the subject will be reviewed for eligibility assessment.

The screening must be performed unless extension of screening period is granted by the CRO/sponsor medical monitor after an evaluation of the impact of the extended period on assessment of efficacy and safety.

Subjects will enter the study center on Day 1 to receive the first administration of IMP and will complete the required assessments and sample collections.

Subjects may be admitted a day prior to Cycle 1 Day 1 dosing and if required stay overnight at the study center on Cycle 1 Day 1, based on Investigator's discretion. Subjects will complete the assessments on Cycle 1 Day 2 and may remain in the study center overnight for observation, at the discretion of the Investigator. Subjects will return for follow-up assessments in Cycle 1

Cycle 2 will have similar sample collections and subjects will be required to return to the study center for other follow-up assessments. From Cycle 3 onwards, subjects will only be required to return to the study center once every

Note: The last observation/evaluations for each cycle may coincide with the Day 1 of next cycle e.g., Cycle 6 Day observation may coincide with Cycle 7 Day 1). samples will be collected on the day of the study visit from Cycle 3 onwards.

Subjects will remain on study treatment for approximately 60 months (i.e.: 5 years from 1st K0706 dosing), or until intolerance, subject withdraws from the study, or progression of disease. Subjects who discontinue the study will be followed up for survival (survival assessment includes information about subject survival and anticancer therapies) every 3 months (\pm 2 weeks) after the IMP discontinuation till 60 months from their first dose of K0706 or until death, withdrawal of consent, or the end of the study, whichever comes first.

Treatment beyond 60 months will be considered, provided the Investigator considers that the subject is benefiting from K0706 therapy. Subjects who continue to receive K0706 beyond 60 months will be followed up for safety, survival and response assessment. Information about subject's survival and disease response will be collected at the follow up visits every 3 months (\pm 2 weeks) in these subjects. For additional details on the study conduct please refer to the applicable protocol sections and schedule of assessments.

A subject experiencing any study drug associated toxicities may continue on therapy at the same dose if disease control is achieved or with a reduced dose of K0706 at the Investigator discretion. Subjects who experience a toxicity and recover, may be treated, at the Investigator's discretion, at the same dose or next lower dose level until disease progression or occurrence of other events requiring further dose reduction.

Additional dose reductions can be

implemented upon consultation between Sponsor's medical monitor, treating investigator and the subject. For further guidance on dose reduction and delay refer to Section 7.4.2. [REDACTED]
 [REDACTED]

Study End points: Part C

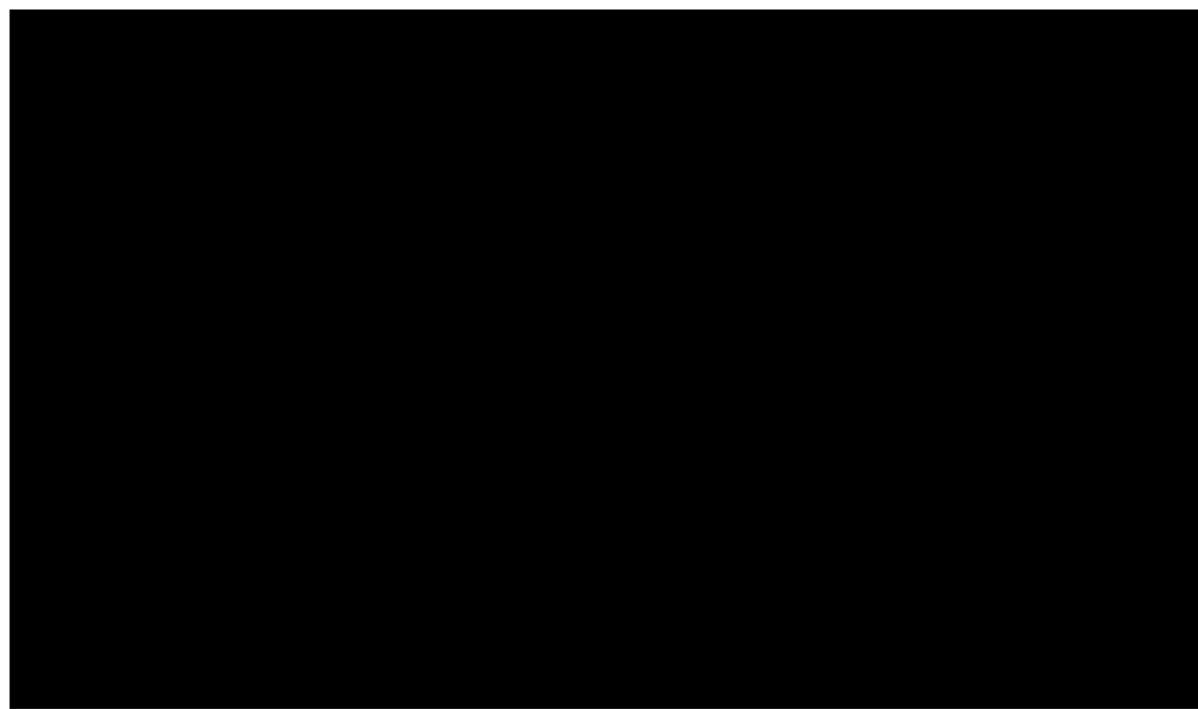
Primary Endpoints

- Cohort A: For CML subjects in CP at study entry: Major Cytogenetic Response (MCyR), defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR). (CP subjects in CCyR are not eligible for this study)
- Cohort B: For CML subjects in AP at study entry: Major Hematologic Response (MaHR), defined as complete hematologic response (CHR) or no evidence of leukemia (NEL). (AP subjects in MaHR are not eligible for this study)
- Cohort C: For CML subjects in BP at study entry: MaHR, consisting of CHR or NEL. (BP subjects in MaHR are not eligible for this study)

Secondary Endpoints

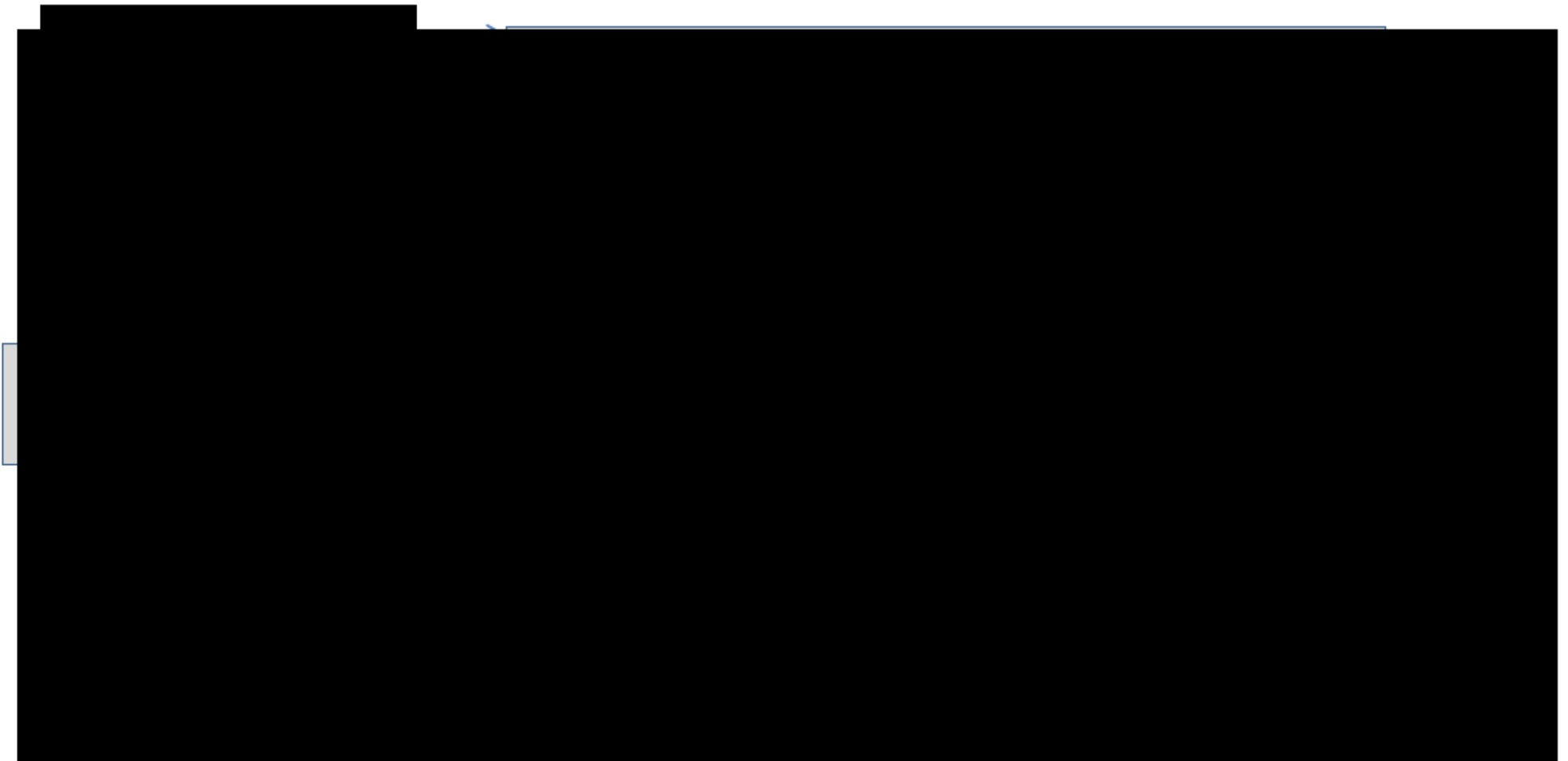
- In subjects with CML-CP
 - Hematological responses: Proportion of subjects who achieve or maintain complete hematological response
 - Cytogenetic response: Proportion of subjects who achieve CCyR
 - Molecular responses: Proportion of subjects who achieve MMR
- In subjects with CML-AP or CML-BP
 - Cytogenetic responses: Proportion of subjects who achieve CCyR, PCyR
 - Molecular responses: Proportion of subjects who achieve MMR
- In all subjects: Safety and tolerability in terms of incidence, severity and seriousness of treatment emergent AEs
- In all subjects: Time to response, duration of response, PFS and OS



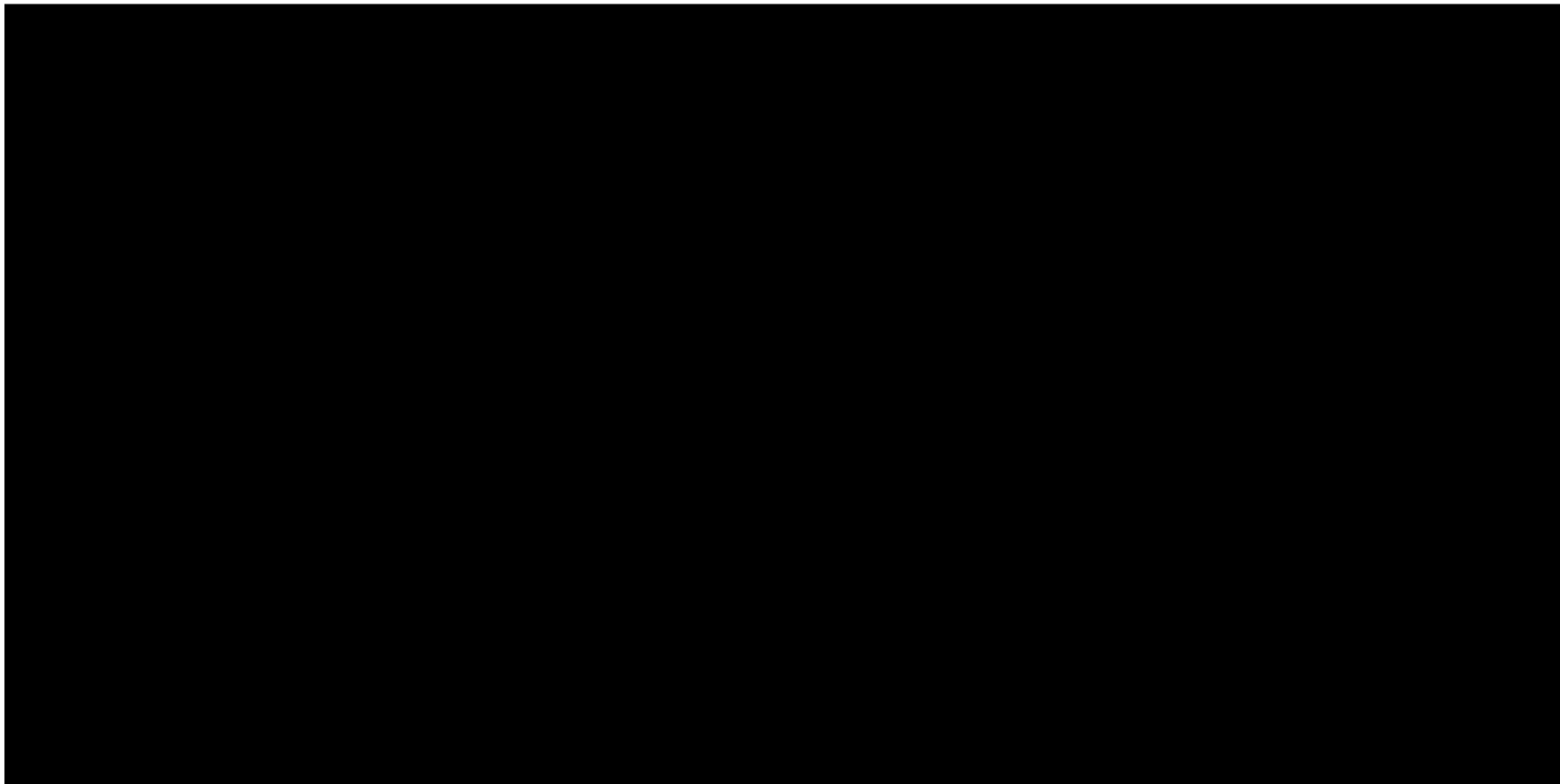


Abbreviations: D: Day, DLT: Dose limiting toxicity, MTD: Maximum tolerated dose.





- A. If medically warranted, subjects may be admitted to the study center overnight on Cycle 1 Day 1.
- B. The last observation and assessments for each cycle will coincide with the Day 1 of next cycle (the window period for Day 1 of every cycle is ± 3 days)



Abbreviations: IMP: Investigational medicinal product

A. If medically warranted, subjects may be admitted to the study center overnight on Cycle 1 Day 1.

B. The last observation and assessments for each cycle will coincide with the Day 1 of next cycle (the window period for Day 1 of every cycle is ± 3 days)

Criteria for Inclusion:

Part B

Inclusion Criteria:

Subjects may be included in the study if they meet all of the following criteria:

1. Willing and able to give written/signed, and dated, informed consent (or by legally acceptable representative/impartial witness when applicable; inclusion of subjects needing legally acceptable representative/impartial witness will be in compliance to the enrolling country's regulatory requirement) and is available for the entire study.
2. Willing and able to comply with the scheduled visits, treatment plan, laboratory testing, study procedures, and restrictions and be accessible for follow-up
3. Subjects diagnosed with Ph+ CML-CP, Ph+ CML-AP, Ph+ CML-BP or Ph+ ALL who are refractory or intolerant to at least 3 TKIs or are not eligible (e.g.: due to comorbidities, hypersensitivity to excipients, lack of insurance coverage) for their local country's regulatory approved and medically appropriate TKIs (e.g., a TKI that is effective against mutations in the patient's tumor).
4. Male or female aged ≥ 18 years
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
6. [REDACTED]

7. Subjects of childbearing potential must practice an medically acceptable effective method of birth control as judged by the Investigator:
 - a. Medically acceptable methods of birth control include the use any of the effective birth control methods as listed below -
 - i. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
 - ii. Progestogen-only hormonal contraception associated with inhibition of ovulation
 - iii. Placement of an IUD/ intra-uterine hormone releasing system. Consideration should be given to the type of device or system being used, as there are higher failure rates quoted for certain types, e.g., steel or copper wire
 - iv. Intrauterine hormone-releasing system (IUS)
 - v. Same sex partner, a vasectomized partner/bilateral tubal occlusion.
 - b. The contraception should have been used continually within the past 3 months and the subject has to agree to continued use during the study and for 3 months after the last IMP administration.
 - c. To adopt another birth control method, or a double-barrier method which consists of a combination of any 2 of the following: diaphragm, cervical cap, condom, or a spermicide. The barrier method must be used in combination with another highly effective, non-barrier method (such as mentioned in Inclusion criteria # 7a) for at least 2 months prior to study entry and must continue to use contraception for the duration of the study and for 3 months after the last IMP administration.
 - d. Subjects who are postmenopausal for at least 1 year based on history and Investigator's opinion or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy has been performed on the subject). For women < 45 years with menopausal symptoms, the menopause status to be reconfirmed by suitable laboratory tests including FSH level.
8. Male subjects enrolled in the study should not father a child and are advised to prevent passage of semen to their sexual partner during intercourse using an acceptable method as detailed in the Inclusion criteria # 7 and judged by the Investigator for the duration of the study and for 3 months after the last IMP administration.
9. Female subjects of childbearing potential must have a negative pregnancy test (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin).
10. Female subjects must be non-lactating and non-breast-feeding

Exclusion Criteria:

Subjects will be excluded from the study if they meet any of the following criteria:

1. Presence of T315I mutations
*(*Note: Enrollment of subjects bearing T315I mutation will be opened when sufficient plasma levels found to be active preclinically in the T315I clone are achieved)*
2. Any major surgery, as determined by the Investigator, within 4 weeks of IMP administration.
 (Exceptions: Minor procedures such as bone marrow biopsy/aspiration, catheter placements and other procedures which in Investigator's opinion do not compromise subject safety)

3. Inability to swallow oral medication
4. Inability to undergo venipuncture and/or tolerate venous access
5. Evidence of clinically significant organ dysfunction or any clinically relevant deviation from normal in physical examination, ECG findings, vital signs, or clinical laboratory test findings which in the opinion of the investigator may jeopardize the safety of the patient during the study or may interfere with the evaluation of the study drug.
6. Positive tests: urine pregnancy tests (if applicable), HIV
7. History of any relevant allergy/hypersensitivity (including known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the IMP or its excipients)
8. Known history of active hepatitis B or hepatitis C
9. Received any other investigational agent within 30 days or a washout of at least 5 half-lives, whichever is longer, of IMP administration
10. Use of concomitant medication that might influence the results of the study prior to IMP administration and/or anticipated need at any time during the study.
11. Known or suspected history of significant drug abuse as judged by the Investigator.
12. Known or suspected history of alcohol abuse or excessive intake of alcohol in the 12 months prior to study entry.
13. Involvement in the planning and/or conduct of the study (applies to Sponsor, Contract Research Organizations, and study center staff, etc.)
14. [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
15. Malabsorption syndrome or other illness that could affect oral absorption of the IMP
[REDACTED]
[REDACTED]
 - [REDACTED]
[REDACTED]
 - [REDACTED]
[REDACTED]
[REDACTED]
 - [REDACTED]

- d. Prolonged rate-corrected QT Interval (QTcF) on the Screening ECG > 450 msec for males and > 470 msec for females
17. Uncontrolled intercurrent illness including, but not limited to the following: ongoing or active infection, uncontrolled seizure disorder, psychiatric or social circumstances that would limit compliance with study requirements as per the Investigator's discretion
18. Subjects who are eligible for potentially curative therapy that is available, including hematopoietic stem cell transplant
19. Autologous or allogeneic stem cell transplant \leq 3 months prior to Screening; any evidence of ongoing graft versus host disease (GVHD) or GVHD requiring immunosuppressive therapy \leq 28 days prior to the first IMP administration visit
20. Another primary malignancy within the past 3 years or earlier (except for adequately treated non-melanoma skin cancer or cervical cancer in situ)
21. Any condition or illness that, in the opinion of the Investigator, would compromise subject safety or interfere with the evaluation of the safety of the study drug
22. Intake of any restricted medications as described in the study restrictions (Section 6.4.6.1)
23. Any contraindications for repeated bone marrow sample collection
24. Active central nervous system (CNS) disease as evidenced by cytology or pathology. In the absence of active CNS disease, lumbar puncture is not required. History of CNS disease is not exclusionary if CNS disease has been cleared and documented by negative lumbar puncture and other necessary procedures at screening

Part C

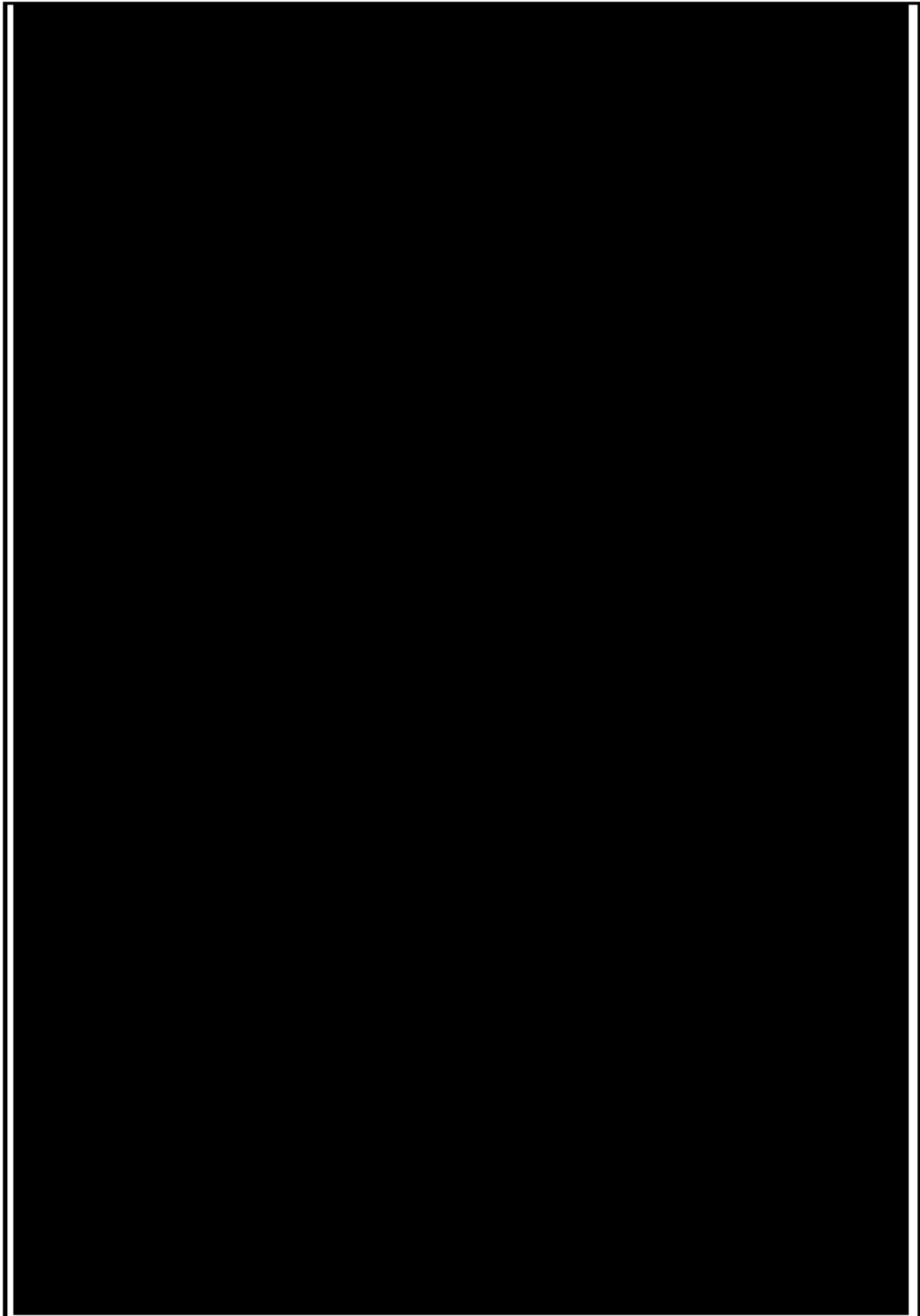
Inclusion Criteria:

Subjects may be included in the study if they meet all of the following criteria:

1. Willing and able to give written/signed, and dated, informed consent (or by legally acceptable representative/impartial witness when applicable; inclusion of subjects needing legally acceptable representative/impartial witness will be in compliance to the enrolling country's regulatory requirement) and is available for the entire study
2. Willing and able to comply with the scheduled visits, treatment plan, laboratory testing, study procedures, and restrictions, and be accessible for follow-up
3. Subjects with Ph+ CML CP, AP or BP who are resistant and/or intolerant to \geq 3 prior TKIs one of which is ponatinib. (Subjects with Ph+ ALL are not included)

[REDACTED]

[REDACTED]



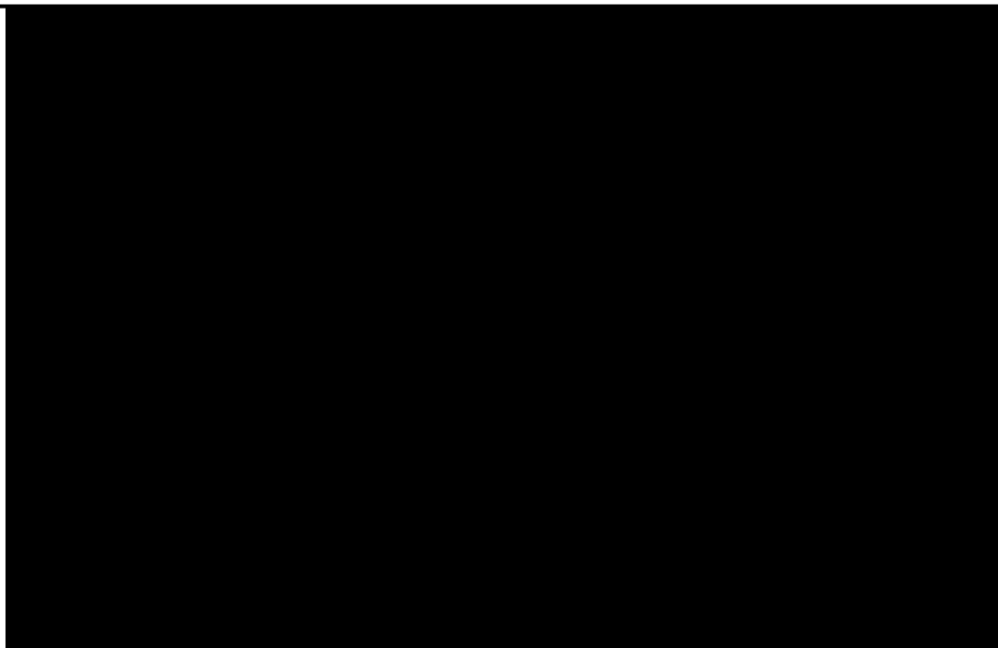
[REDACTED]

[REDACTED]

[REDACTED]

4. Male or female aged ≥ 18 years
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2

■ [REDACTED]
[REDACTED]
[REDACTED]



7. Subjects of childbearing potential must practice a medically acceptable method of birth control as judged by the Investigator:
 - a. Medically acceptable methods of birth control include the use any of effective birth control methods listed below -
 - i. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
 - ii. Progestogen-only hormonal contraception associated with inhibition of ovulation
 - iii. Placement of an IUD/ intra-uterine hormone releasing system. Consideration should be given to the type of device or system being used, as there are higher failure rates quoted for certain types, e.g., steel or copper wire
 - iv. intrauterine hormone-releasing system (IUS)
 - v. same sex partner, a vasectomized partner/bilateral tubal occlusion
 - b. The contraception should have been used continually within the past 3 months and the subject has to agree to continued use during the study and for 3 months after the last IMP administration
 - c. To adopt another birth control method, or a double-barrier method which consists of a combination of any 2 of the following: diaphragm, cervical cap, condom, or a spermicide. The barrier method must be used in combination with another highly effective, non-barrier method (such as mentioned in Inclusion criteria # 7a) for at least 2 months prior to study entry and must continue to use contraception for the duration of the study and for 3 months after the last IMP administration
 - d. Subject is postmenopausal for at least 1 year as per menstrual history or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy has been performed on the subject). For women < 45 years with menopausal symptoms, the menopause status to be reconfirmed by suitable laboratory tests including FSH level.
8. Male subjects enrolled in the study should not father a child and are advised to prevent passage of semen to their sexual partner during intercourse using an acceptable method as detailed in the

Inclusion criteria # 7 and judged by the Investigator for the duration of the study and for 3 months after the last IMP administration

9. Female subjects of childbearing potential must have a negative pregnancy test (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin).
10. Female subjects must be non-lactating and non-breast-feeding

Exclusion Criteria:

Subjects will be excluded from the study if they meet any of the following criteria:

1. Presence of T315I mutation
2. Any major surgery, as determined by the Investigator, within 4 weeks of IMP administration (Exceptions: Minor procedures such as bone marrow biopsy/aspiration, catheter placements and other procedures which in Investigator's opinion do not compromise subject safety)
3. Inability to swallow oral medication
4. Inability to undergo venipuncture and/or tolerate venous access
5. Evidence of clinically significant organ dysfunction or any clinically relevant deviation from normal in physical examination, ECG findings, vital signs, or clinical laboratory test findings which in the opinion of the investigator may jeopardize the safety of the patient during the study or may interfere with the evaluation of the study drug.
6. Positive tests: urine pregnancy tests (if applicable), HIV
7. History of any relevant allergy/hypersensitivity (including known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the IMP or its excipients)
8. Known history of active hepatitis B or hepatitis C
9. Received any other investigational agent within 30 days or a washout of at least 5 half-lives, whichever is longer, of IMP administration
10. Use of concomitant medication that might influence the results of the study prior to IMP administration/or anticipated need any time during the study
11. Known or suspected history of significant drug or alcohol abuse as judged by the Investigator
12. Known or suspected history of alcohol abuse or excessive intake of alcohol in the 12 months prior to study entry
13. Involvement in the planning and/or conduct of the study (applies to Sponsor, Contract Research Organizations, and study center staff, etc.)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

15. Active central nervous system (CNS) disease as evidenced by cytology or pathology. In the absence of active CNS disease, lumbar puncture is not required. History of CNS disease is not exclusionary if CNS disease has been cleared and documented by negative lumbar puncture and other necessary procedures at screening.

16. Malabsorption syndrome or other illness that could affect oral absorption of the IMP

17. History of acute pancreatitis within 1 year of study or history of chronic pancreatitis

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

19. Uncontrolled intercurrent illness including, but not limited to the following: ongoing or active infection, uncontrolled seizure disorder, psychiatric or social circumstances that would limit compliance with study requirements or illness that, in the opinion of the Investigator, would compromise subject safety or interfere with the evaluation of the safety of the study drug

20. Subjects who are eligible for potentially curative therapy that is available, including hematopoietic stem cell transplant

21. Autologous or allogeneic stem cell transplant ≤ 3 months prior to Screening; any evidence of ongoing graft versus host disease (GVHD) or GVHD requiring immunosuppressive therapy ≤ 28 days prior to the first IMP administration visit

22. Another primary malignancy within the past 3 years or earlier (except for adequately treated non-melanoma skin cancer or cervical cancer in situ)

23. Any contraindications for repeated bone marrow sample collection

24. Prior exposure to K0706 therapy as a participant in Part B of the protocol

Test Product, Dose and Route of Administration:

K0706 capsules

[REDACTED]

Formulation: [REDACTED] capsule of K0706 [REDACTED].

[REDACTED]

Storage: Store at 20°C to 25°C (68°F to 77°F), with excursions permitted from 15°C to 30°C (59°F to 86°F)

Part B: K0706 capsules will be self-administered. [REDACTED]

[REDACTED] The initial administered dose will be the dose from Part A where acceptable safety was observed (e.g., 2 or more subjects do not develop Grade 2 or higher AEs [AEs; in the same biologic system that are not clearly and incontrovertibly related to something other than the IMP]) in an 8 subject cohort, or no subject develops AE Grade 3 or higher (that is not clearly and incontrovertibly related to something other than the IMP). Assuming minimal toxicity, an expected dose escalation would proceed as mentioned in the table below. The decision to proceed to the next dose escalation will be determined by the Sponsor and Part B Principal Investigators.

| [REDACTED] | [REDACTED] | [REDACTED] |
|------------|------------|------------|
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |

Once 2 subjects experience a Grade 2 or 1 subject experiences Grade 3 or 4 toxicity (unless the AE is clearly and incontrovertibly related to underlying disease), further dose escalation steps will be reduced to 40% increments. The capsule composition of these doses will be assembled from the available capsule sizes and the selected dose will be rounded downwards rather than upwards to achieve a dose near the 40% increment. The capsules themselves will not be altered, only the combination of different capsules to be administered, [REDACTED]

Part C: K0706 capsules will be self-administered once daily at dose of 174 mg.

Reference Therapy, Dose and Route of Administration:

Part B

No placebo will be administered.

Part C

No placebo/comparator will be administered

Duration of Treatment:

Part B

Subjects will be provided K0706 capsules to self-administer at home daily at their assigned dose until intolerance, the subject withdraws from the study, or disease progression.

Subject participation will be approximately 60 months [REDACTED]

[REDACTED] Subjects will remain on study treatment for approximately 60 months (i.e., 5 years from 1st K0706 dosing), or earlier in the event of intolerance, the subject withdrawing from the study, or progression of disease. Treatment can be extended beyond 60 months if the subject is benefiting from the therapy as per medical judgment of the investigator.

Part C

Subject participation will be approximately 60 months [REDACTED]

[REDACTED] Subjects will remain on study treatment for approximately 60 months (i.e., 5 years from 1st K0706 dosing), or earlier in the event of intolerance, the subject withdrawing from the study, or progression of disease. Treatment can be extended beyond 60 months if the subject is benefiting from the therapy as per medical judgment of the investigator.

Criteria for Evaluation

Pharmacokinetics:

Part B

Plasma PK parameters of K0706 calculated as appropriate: [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Part C

Plasma PK parameters of K0706 calculated as appropriate: [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Population PK parameters of K0706 will be determined [REDACTED].

Exploratory Assessments:

In Part B & C of the study, serum, blood, and bone marrow-based samples may be collected at specified time points to determine the following:

- BCR-ABL mutation profile at screening
- BCR-ABL mutation profile at progression (should it occur)

Samples for BCR-ABL mutation profiles will be collected during Screening and at progression if observed.

Safety:

The safety and tolerability profile of K0706 in subjects treated on this study will be assessed by physical examination, analysis of frequency, seriousness and intensity of AEs, vital signs (including temperature, heart rate, respiratory rate, and diastolic and systolic blood pressure), ECG, and clinical laboratory tests [including hematology, coagulation, cardiac troponin (for Part B only), biochemistry, and urinalysis].

Adverse events will be assessed based on the NCI CTCAE v4.03 for Part B (v5.0 for Part C) and categorized as serious AEs or non-serious AEs. The relationship of AEs to K0706 will be assessed by the Investigator per the protocol-defined criteria for attribution assessment. Subject performance status will be assessed using the ECOG performance status scale.

All physical examination (PE), medical history-reported, and screening laboratory values considered to be clinically significant and occurring post-consent, unassociated with the study procedures but prior to receiving the first dose of study drug will be classified and graded according to CTCAE nomenclature but will not be considered AEs and entered in subject's medical history. Disease progression will not be considered an AE unless it leads to death or hospitalization in which case it needs to be reported as SAE. For subjects with disease progression, wherein there is a need to initiate alternate therapy for treatment of disease, end of treatment visit can be completed earlier than 30 days; however the 30 day safety follow visit should be completed and the treatment related AEs occurring in the 30 day safety observation period should be reported and/or followed up to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause (i.e. concurrent condition or medication) and the clinical judgment of the Investigator indicates that further evaluation is not warranted.

Statistical Methods

Pharmacokinetic Parameters

Plasma concentrations and PK parameters for K0706 will be listed and summarized by dose cohort using descriptive statistics [REDACTED] in Part B. Additionally, the following evaluations will be done as appropriate:

In Part B, Dose proportionality [REDACTED] will be assessed [REDACTED] for Cycle 1 and Cycle 2. Dose proportionality may also be [REDACTED] evaluated using the [REDACTED], if sufficient data is available (at least n=3) for a given cohort. Steady-state [REDACTED] will be evaluated [REDACTED]. Any additional pharmacokinetic evaluations will be described in the Statistical Analysis Plan (SAP).

In Part C, concentrations from the population PK will be evaluated. The details will be explained in the SAP.

Efficacy Parameters:

In Parts B : Hematological response, Cytogenetic response and Molecular response rates will be assessed for efficacy according to criteria mentioned in Appendix I (Section 13.1). All subjects will be followed for up to approximately 60 months after the first dose of K0706. Efficacy analysis will include all subjects in the efficacy analysis set.

For Part C: Hematological response, Cytogenetic response and Molecular response rates will be assessed for efficacy according to criteria mentioned in Appendix I (Section 13.1). All subjects will be followed for up to approximately 60 months after the first dose of K0706.

All efficacy analysis will be performed separately per Cohort (designated from Cohort A to C), and will include all subjects in the efficacy analysis set (Section Efficacy analysis set 6.8.3.2). Primary and secondary efficacy response rates will be summarized by both point estimates and estimation of [REDACTED] confidence intervals. Continuous PD endpoints will be summarized using descriptive statistics [REDACTED], and time-to-event endpoints will be summarized using [REDACTED] and using [REDACTED]. Detailed information for censoring rules for PFS and OS will be incorporated in the SAP. More detailed information about estimation of treatment effects, summarization of data, graphical representations, and analysis conventions will be provided in the SAP. PD evaluations if undertaken will be described in the Statistical Analysis Plan.

Safety Parameters:

In general, descriptive summaries will be presented for the safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum.

Categorical variables will be summarized using frequency counts and percentages. For time-to-event variables other percentiles will be presented.

The change from baseline in ECG parameters [REDACTED], laboratory parameters, and vital signs will be examined by dose cohort and scheduled visit.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities and will be summarized by System Organ Class and Preferred Term. In addition, summaries of AEs by intensity, seriousness, frequency, and relationship to IMP will be presented.

Formal testing of treatment effects will not be performed. However, where appropriate, some measures will be summarized by both point estimates and estimation of [REDACTED] confidence intervals. More detailed information about the estimation of treatment effects, summarization of data, graphical representations, and analysis conventions will be provided in the Statistical Analysis Plan.

4 LIST OF ABBREVIATIONS

| | |
|-------------------------|--|
| λ_z | Lambda_z |
| ABL | Abelson leukemia |
| AE | Adverse event |
| ALL | Acute lymphoblastic leukemia |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase |
| AUC | Area under the plasma concentration-time curve |
| AUC ₍₀₋₂₄₎ | Area under the plasma concentration-time curve of the analyte from time zero (predose) to 24 hours postdose |
| AUC _(0-inf) | Area under the plasma concentration-time curve of the analyte from time zero (predose) extrapolated to time infinity |
| AUC _(0-last) | Area under the plasma concentration-time curve of the analyte in the sampled matrix from zero (predose) to last quantifiable concentration |
| AUC _(0-t) | Area under the plasma concentration-time curve of the analyte from time zero (predose) to time t |
| AUC _(0-tau) | Area under the plasma concentration-time curve over the dosing interval |
| BCR | Breakpoint cluster region |
| CCyR | Complete Cytogenetic Response |
| CHR | Complete Hematologic Response |
| CL/F | Apparent systemic clearance |
| CML | Chronic Myeloid Leukemia |
| CML-AP | CML accelerated phase |
| CML-BP | CML blast phase |
| CML-CP | CML chronic phase |
| C _{max} | Maximum observed plasma concentration |
| CNS | Central nervous system |
| CTCAE | Common Terminology Criteria for Adverse Events |
| C _{trough} | Trough plasma concentration |
| CVS | Cardiovascular system |
| CYP | Cytochrome |
| D | Day |
| DLT | Dose limiting toxicity |
| DMSO | Dimethylsulfoxide |
| DNA | Deoxyribonucleic acid |
| DSMB | Data Safety Monitoring Board |
| EC ₅₀ | Half maximal effective concentration |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EDC | Electronic data capture |

| | |
|------------------|---|
| EoT | End of Treatment |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GVHD | Graft versus host disease |
| HEK | Human embryonic kidney |
| hERG | Human Ether-a-go-go-related gene |
| HIV | Human immunodeficiency virus |
| IB | Investigator's Brochure |
| IC ₅₀ | Half maximal inhibitory concentration |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IMP | Investigational medicinal product |
| INR | International normalized ratio |
| IUD | Intrauterine device |
| K _d | Dissociation constant |
| LD ₀ | Non-lethal dose |
| LVEF | Left ventricular ejection fraction |
| MAD | Multiple Ascending Dose |
| MaHR | Major Hematologic Response |
| MCyR | Major Cytogenetic Response |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial infarction |
| MMR | Major Molecular Response |
| mRNA | Messenger ribonucleic acid |
| MTD | Maximum tolerated dose |
| NCI | National Cancer Institute |
| NOAEL | No-observed-adverse-effect-level |
| NYHA | New York Heart Association |
| PCR | Polymerase chain reaction |
| PCyR | Partial Cytogenetic Response |
| PD | Pharmacodynamic |
| PD-LTC | Patient-derived long-term cultures |
| Ph+ | Philadelphia chromosome positive |
| PK | Pharmacokinetic |
| PR interval | Interval between the beginning of the P wave and the beginning of the QRS complex of an ECG |
| PTT | Partial thromboplastin time |
| aPTT | Activated partial thromboplastin time |
| QRS | Series of deflections in an ECG that represent electrical activity generated by ventricular depolarization prior to contraction of the ventricles |
| QT interval | Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle |

| | |
|-----------|---|
| QTc | Rate-corrected QT interval |
| RP2D | Recommended Phase 2 dose |
| RR | R wave-to-R wave |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | Sprague-Dawley |
| SPARC | Sun Pharma Advanced Research Company |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{1/2}$ | Apparent terminal half-life |
| TIA | Transient ischemic attack |
| TKI | Tyrosine kinase inhibitor |
| t_{max} | Time to C_{max} |
| ULN | Upper limit of normal |
| US | United States |
| V_z/F | Apparent volume of distribution |
| WBC | White blood cell |
| WOCBP | Women of childbearing potential |

5 INTRODUCTION FOR PARTS B & C

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder representing about 15% to 20% of adult leukemias. The underlying cause of CML is the breakpoint cluster region-Abelson leukemia (BCR-ABL) fusion oncoprotein which results from a reciprocal t(9;22) chromosomal translocation in hematopoietic stem cells. This chromosomal abnormality, known as the Philadelphia chromosome (Ph+), is present in about 95% of all patients with CML, as well as about 20% to 25% of adult patients with acute lymphoblastic leukemia (ALL). The translocation leads to the fusion of the breakpoint cluster region (BCR) coding sequence with the tyrosine kinase coding region of Abelson leukemia (ABL). This fusion event results in the constitutive activation of ABL kinase activity. The BCR-ABL activates multiple downstream pathways that contribute to the growth and survival of cells. The disease is characterized and classified by phases: chronic phase, accelerated phase, or blast phase. The use of a tyrosine kinase inhibitor (TKI) that targets BCR-ABL is a well-established and highly effective strategy for sustained disease control in Ph+ CML. Mutations in the kinase domain of BCR-ABL that impede effective inhibitor binding is the primary mechanism of resistance to currently available agents in particular, the T315I gatekeeper mutant is resistant to all first and second line approved BCR-ABL inhibitors. Sun Pharma Advanced Research Company (SPARC) Limited plans to conduct a Phase 1/2 open-label, dose escalation, safety/tolerance, and pharmacokinetic (PK) study in patients with refractory or advanced CML and other refractory hematologic malignancies other than lymphoma. The study's primary outcome measures include identification of the recommended Phase 2 dose (RP2D) in Part B of the study and efficacy outcomes for Part C of the study.

Background Information

K0706 is a novel BCR-ABL TKI developed by SPARC. Studies of K0706 were conducted with either a base K0706 or its melt extrusion (ME) formulation. The ME formulation with some additional non-bioactive excipients is to be used for further development.

Sun Pharma Advanced Research Company has elucidated the chemical structure of the manufactured drug substance and characterized its potential impurities. The drug substance exists in only 1 polymorphic form and was confirmed as a single crystalline form in solid state characterization studies.

The pre-clinical testing strategy for K0706 was designed to support its development for the treatment of patients with CML or Ph+ ALL. The preclinical and clinical studies that have been completed to date are summarized in the Investigator's Brochure (IB).

Overall, pharmacology, PK, and safety pharmacology data indicate that K0706 has [REDACTED] on [REDACTED] at [REDACTED] ranges.

In agreement with its *in vitro* profile, K0706 shows [REDACTED] in its *in vivo* models based on [REDACTED]. It shows [REDACTED] in oral administration in [REDACTED]. It has [REDACTED] effect on the central nervous system (CNS), cardiovascular system (CVS), and respiratory functions at several multiples of [REDACTED] doses.

The development program for K0706 seeks the indication for the treatment of adult subjects with CML-CP, CML-AP, or CML-BP that is resistant or intolerant to prior TKI therapy.

The clinical study is divided as:

Part A: Single ascending dose study in healthy human volunteers to understand the bioavailability of K0706 and support multiple ascending dose (MAD) study in subjects with BCR-ABL malignancies. This study is completed and for details of the study please refer to Appendix III Section 13.3.

Part B: MAD study in subjects with CML-CP, CML-AP, CML-BP or Ph+ ALL that is resistant or intolerant to prior TKI therapy, to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of K0706.

Part C: Efficacy and safety study in subjects with CML-CP, CML-AP, or CML-BP that is resistant or intolerant to ≥ 3 prior TKIs one of which includes ponatinib at the RP2D.

5.1 NON-CLINICAL OVERVIEW

5.1.1 Pharmacology

A series of *in vitro* and *in vivo* studies were carried out to evaluate the action and efficacy of K0706. These included 8 non-Good Laboratory Practice (GLP) *in vitro* studies, and 3 non-GLP *in vivo* studies in mouse models of Ph+ CML and ALL. In addition, the pharmacological safety of K0706 was evaluated in 1 GLP study in the CNS, 2 non-GLP and 2 GLP studies in the CVS, and 1 GLP study in the respiratory system. Refer to Investigator's Brochure (IB) for more details.

5.1.1.1 In Vitro Primary Pharmacodynamics

K0706, developed as a BCR-ABL TKI, was evaluated for its [REDACTED] activity on the native ABL as well as its mutant forms in [REDACTED]. Conventional [REDACTED], using [REDACTED] and [REDACTED] as readouts, were used to derive [REDACTED] values and a [REDACTED]. [REDACTED] was used to derive [REDACTED] values. K0706 [REDACTED].

Observed [REDACTED] values ranged from [REDACTED] for K0706, compared with 0.3 to 0.9 nM for ponatinib. Observed [REDACTED] values ranged from [REDACTED] for K0706, compared with 0.10 to 1.70 nM for ponatinib.

In the cell line based assays, K0706 demonstrates in vitro [REDACTED] as observed in Table 5-1. Additional information on the anti-proliferative activity Table 5-2 is included in the IB.

[REDACTED]

[REDACTED]

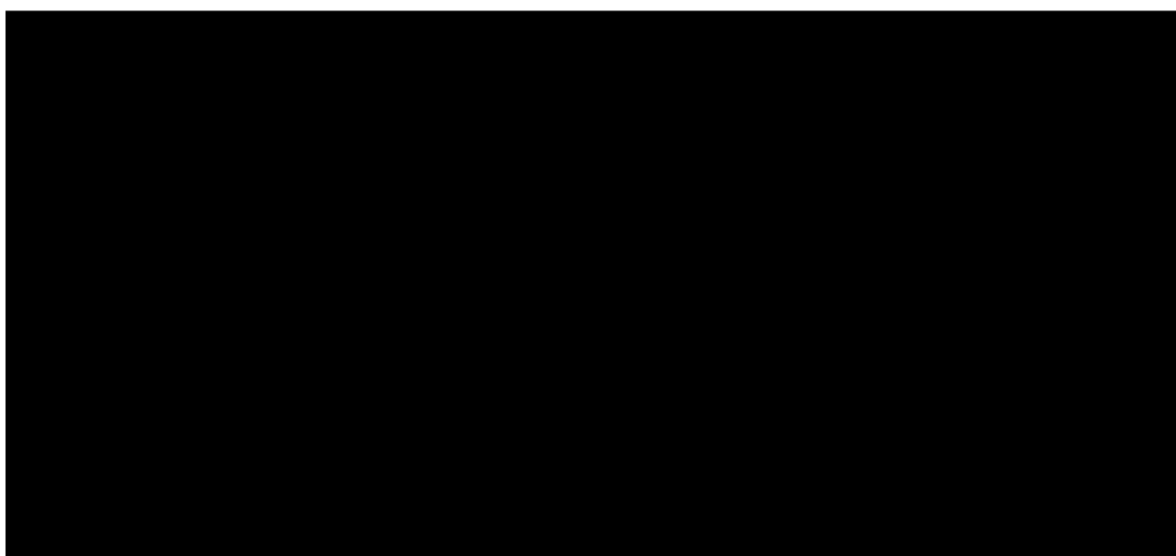
[REDACTED]

[REDACTED]

5.1.1.2 In Vivo Primary Pharmacodynamics

Anti-leukemic activity of K0706 has been demonstrated in [REDACTED] of Ph+ CML and Ph+ ALL as depicted in Table 5-3

[REDACTED]



5.1.1.3 Secondary Pharmacodynamics

Secondary pharmacodynamics were investigated through an *in vitro* high throughput screening that involved [REDACTED] cellular targets, including [REDACTED]. There was [REDACTED] significant effect on the majority of cellular targets tested. However, K0706 demonstrated [REDACTED]

5.1.1.4 Safety Pharmacology

The non-clinical safety data is available in the IB. Key findings from the IB are mentioned here.

5.1.1.4.1 CNS safety

The safety of single-dose orally administered K0706 was evaluated in the CNS using an [REDACTED]. Dose-dependent statistically significant differences were observed in the test and placebo group.

5.1.1.4.2 Cardiovascular Safety

Cardiovascular safety of K0706 was evaluated through [REDACTED] *in vitro* studies and [REDACTED] *in vivo* study. The available *in vitro* and animal data [REDACTED] suggest a potential for prolongation of QTc interval or any disturbance of ECG rhythm and waveform morphology.

5.1.1.4.3 Respiratory Safety

A respiratory safety study was conducted in [REDACTED] by evaluating respiratory functions using [REDACTED]. There were [REDACTED] statistically significant

changes in respiratory parameters when compared with baseline. Overall, there were [REDACTED] statistically significant changes observed due to K0706 administration in the [REDACTED].

5.1.2 Pharmacokinetics

Pharmacokinetic parameters of K0706 have been examined *in vitro* in a [REDACTED] and *in vivo* in a [REDACTED] studies in [REDACTED]. [REDACTED] has been performed. Four [REDACTED] evaluated K0706 for [REDACTED].

5.1.2.1 In Vitro Absorption

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

5.1.2.2 In Vivo Absorption

[REDACTED]
[REDACTED] Table 5-4 and Table 5-5 summarize the key findings of these studies. For additional details refer to IB.

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The absolute bioavailability was estimated to range from [REDACTED] and [REDACTED] across the 3 doses. These results indicated that the absolute bioavailability of K0706 was [REDACTED] in the [REDACTED] state than in the [REDACTED] state in [REDACTED].

| | | | |
|------------|------------|------------|------------|
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |

5.1.2.3 In Vitro Protein Binding

Serum protein binding of K0706 in [REDACTED] was evaluated using [REDACTED]. At K0706 concentrations ranging from [REDACTED], K0706 was [REDACTED] in all species, independent of concentration.

5.1.2.4 In Vitro Metabolism

[REDACTED] in vitro studies were completed to evaluate K0706 for [REDACTED].
 In [REDACTED], K0706 was evaluated for its [REDACTED] on a panel of [REDACTED]. Concentrations ranging from [REDACTED] were tested. K0706 exerted [REDACTED] at all concentrations tested. For [REDACTED], approximately [REDACTED] was observed at a K0706 concentration of [REDACTED], while [REDACTED] was observed for concentrations of K0706 [REDACTED]. K0706 [REDACTED] appear to be a potent direct or time-dependent [REDACTED] of any of the above-mentioned [REDACTED]. However, K0706 appeared to be a direct and time-dependent [REDACTED] of [REDACTED] with approximately [REDACTED] inhibition at concentrations of K0706 [REDACTED] for [REDACTED] and approximately [REDACTED].

5.1.2.5 Toxicology

The potential toxicity of K0706 has been studied in [REDACTED]
 [REDACTED]
 [REDACTED]. The potential [REDACTED] of K0706 has
 been evaluated in [REDACTED]
 [REDACTED]. The potential [REDACTED]
 toxicity of K0706 has been studied in [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED].

5.1.3 Toxicity Studies

5.1.3.1 Single Dose Toxicity

The single-dose toxicity of K0706 was evaluated in [REDACTED]
 [REDACTED]
 [REDACTED] Refer to IB for
 additional details.

5.1.3.2 Repeat Dose Toxicity

A pivotal [REDACTED]
 [REDACTED] This study also served to establish the [REDACTED]
 [REDACTED] in humans. [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]. Blood concentrations at this
 dose were a [REDACTED].

In a [REDACTED] study, [REDACTED] were treated with placebo or K0706 at [REDACTED]
 [REDACTED] clinical signs were observed in any animal but there was a reversible
 [REDACTED]
 [REDACTED] for males and females was established at [REDACTED]
 [REDACTED]

5.1.3.3 Genotoxicity, Reproductive and Developmental Toxicity

K0706 was evaluated for potential genotoxicity, cytogenetic and mutagenetic
 potential. There were [REDACTED] positive mutagenic effects of K0706 at any concentration tested
 when compared with the vehicle control. The potential reproductive and developmental
 toxicity of K0706 has been studied in [REDACTED]. The high dose K0706 led
 to [REDACTED]
 [REDACTED]

5.2 CLINICAL OVERVIEW : PARTS A & B

Part A consisted of a SAD study in healthy male subjects followed by a food-effect bioavailability study.

Part A of the study aimed to examine the safety and tolerability of single oral doses of K0706 in healthy male subjects. In the Part A SAD study, a total of [REDACTED] subjects were randomized to treatment with [REDACTED] subjects each receiving K0706 ([REDACTED]) and [REDACTED] subjects receiving placebo. All subjects received a single oral administration of the IMP with [REDACTED] subjects completing the study and [REDACTED] being lost to follow-up.

Subjects receiving K0706 were either [REDACTED] males with mean age group ranging from [REDACTED]. The mean age of subjects was [REDACTED] years in the placebo group.

Following oral administration, K0706 at [REDACTED] was absorbed [REDACTED] reaching peak plasma concentrations of [REDACTED] respectively within range of [REDACTED] hours. Dose-related [REDACTED] in K0706 plasma exposure ([REDACTED]) were observed. Dose normalized geometric mean clearance [REDACTED] (range [REDACTED]) was [REDACTED] of dose. The geometric mean [REDACTED] ranged from [REDACTED] hours across the [REDACTED] doses, while the clearance [REDACTED] ranged from [REDACTED], and volume of distribution [REDACTED] ranged from [REDACTED]. Additional details included in IB.

[REDACTED] deaths or SAEs were reported in Part A of the study and [REDACTED] subjects were discontinued due to AEs. Overall, [REDACTED] subjects in the K0706 group and [REDACTED] subjects in the placebo groups reported Treatment Emergent Adverse Events (TEAE). Of the reported TEAEs in the K0706 treatment group, [REDACTED] TEAEs were related (i.e.: probably/possibly) to K0706 administration [i.e.: Abdominal Pain ([REDACTED]), Headache ([REDACTED]), and Somnolence ([REDACTED])]. All reported TEAEs including the TEAEs related with K0706 administration were considered to be mild in severity and resolved without sequel.

No safety concerns based on laboratory measurements, vital signs or ECGs were reported. The Part A [REDACTED] study was a randomized, open-label 2 period cross-over study [REDACTED]

[REDACTED] The clinical capsule formulation of K0706 was studied in [REDACTED] healthy, [REDACTED] subjects at [REDACTED] and in another group of [REDACTED] subjects at the [REDACTED]. When a single [REDACTED] K0706 capsule was administered with a [REDACTED] the mean [REDACTED] was approximately [REDACTED]

Considering the changes to the [REDACTED] which drive the long term efficacy and tolerability in

chronic dosing regimens, the [REDACTED] While, the [REDACTED]-effect remains limited to [REDACTED] considering the heavily pre-treated relapsed CML study population, the clinical study protocol (CLR_15_03: Parts B and C) for CML recommendation dosing of K0706 should be preferably taken after [REDACTED], the subjects should maintain approximately [REDACTED] before and after K0706 dosing in all cycles. Additional PK details are included in IB. [REDACTED] treatment related SAEs were noted. [REDACTED] deaths or SAEs were reported in Part A of the study and [REDACTED] subjects were discontinued due to AEs. [REDACTED] safety concerns based on laboratory measurements, vital signs or ECGs were reported.

Part B consists of dose escalation in subjects with relapsed or TKI intolerant Ph + CML and ALL which includes clinical dose refining in subjects with relapsed or TKI intolerant Ph + CML. The study is currently ongoing.

The objective of this study is to establish safety and MTD or RP2D of K0706 and evaluate preliminary efficacy outcomes to set-up schedule for pivotal investigational plan.

As of 18 Jul 2019, [REDACTED] subjects with relapsed Ph + CML and/or ALL have been treated with oral daily dose of K0706 capsules at doses ranging from [REDACTED]. Currently [REDACTED] subjects have been enrolled at [REDACTED] mg in the dose escalation cohort.

Subject diagnosis in the [REDACTED] subjects included [REDACTED] subjects with Ph+ CML ([REDACTED]). The study consisted of heavily pre-treated population: 83% of subjects had failure/intolerance to ≥ 3 TKIs; 100% of subjects had failed at least 1 TKI (i.e.: imatinib). BCR-ABL mutations were reported in 46% [REDACTED] patients entering the study and confirmed in 37% [REDACTED] patients at baseline.

Details on subject demographics and disease status are included in Table 5-7.

[REDACTED]

[REDACTED]

Dosing for K0706 began with [REDACTED] and escalated up to [REDACTED] dose limiting toxicities were observed up to dosing at [REDACTED]. In the [REDACTED] cohort, consisting of [REDACTED] evaluable subjects, [REDACTED] was identified. This DLT finding was confounded with history of leukemic deposits in the central nervous system and extra-medullary spread of the disease on investigational therapy. In the [REDACTED] cohort consisting of [REDACTED] evaluable subjects a single DLT- Missing $\geq 25\%$ of the study drug doses in cycle [REDACTED] on account of [REDACTED] was observed. [REDACTED] resolved with medication and subject re-started at [REDACTED] of K0706, tolerated it well. Subject has completed > [REDACTED]. The [REDACTED] cohort consisted of [REDACTED] subjects, all of whom tolerated the dose well. The [REDACTED] cohort comprised of [REDACTED] subjects who completed the DLT period. [REDACTED] more subjects were added to this group on basis of version 10 amendment 10 of the protocol to understand safety and efficacy, with [REDACTED] DLTs reported. The next dose was initiated at [REDACTED] in [REDACTED] subjects all of whom completed the DLT period [REDACTED] safety observations. The next dosing cohort was [REDACTED] mg which enrolled [REDACTED] subjects. Of these [REDACTED] subjects, one subject had [REDACTED]. Both these events were DLTs as per the criteria of missing $\geq 25\%$ of dose in Cycle 1 and required dose reduction. Based on the iDMC recommendation, it was decided to continue dose escalation at an intermediate dose of [REDACTED]. Currently, enrolment for [REDACTED] mg dose escalation cohort is ongoing, and there are [REDACTED] subjects in this cohort. All [REDACTED] subjects have completed the DLT period without any adverse events attributed to K0706.

Over all the doses studied, K0706 was well-tolerated with treatment related AEs largely limited to Grade 1-2. A total of [REDACTED] AEs were reported in [REDACTED] subjects. Out of [REDACTED] TEAEs, [REDACTED] TEAEs ([REDACTED]) were related to K0706 while [REDACTED] TEAEs ([REDACTED]) were unrelated to K0706. The most common AEs that occurred in [REDACTED] of the subjects included predominantly disorders of the [REDACTED] and [REDACTED] and [REDACTED] disorders (limited to grade 1 and 2). Treatment related [REDACTED] AEs included [REDACTED] of any grade experienced by [REDACTED] subjects ([REDACTED]), [REDACTED] any grade experienced by [REDACTED] subjects ([REDACTED]). A total of [REDACTED] treatment related SAEs have been reported and include: [REDACTED] in a subject dosed at [REDACTED] and moderate [REDACTED] in a subject dosed at [REDACTED].

Early signs of anti-leukemic activity have been observed in the subjects treated with K0706 as listed in Table 5-8.

[REDACTED]

[REDACTED]

The available preclinical and early efficacy and safety observed in Part B form the rationale to initiate Part C (Pivotal study) for K0706 in the subjects with Ph+ CML refractory or intolerant to ≥ 3 TKIs prior TKIs.

6 PART B

This study will be performed in compliance with the protocol, ICH GCP and applicable regulatory requirements. Aspects of the study concerned with the IMP will meet the requirements of the appropriate regulations.

6.1 RATIONALE

Rationale for Starting Dose and Schedule

The [REDACTED] showed a [REDACTED]
[REDACTED] A [REDACTED] was conducted in [REDACTED]
[REDACTED] mortality or severe clinical signs were observed up to a dose of [REDACTED]
[REDACTED]

Based on these findings, the human equivalent dose was calculated from the [REDACTED]
[REDACTED] of K0706. Upon application of the appropriate conversion factors and safety factors as recommended in the US FDA Guidance for Industry (2005), Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Subjects, a starting dose of [REDACTED] K0706 will be used for this first-in-human study.

In more detail, to estimate the potential human exposure at the [REDACTED] starting dose, [REDACTED] was performed on the [REDACTED] data (which used the [REDACTED] formulation) from the [REDACTED]. The [REDACTED] approach was based on the [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED] These findings provide additional safety margin support for the starting dose. There is variability in the data between species, and the starting dose and schedule were selected conservatively to protect subject safety.

Subsequent to these PK studies using [REDACTED] was added to the clinical formulation to facilitate dissolution. [REDACTED] is generally recognized as a safe excipient. The estimated absolute bioavailability of the original [REDACTED] formulation ranged from [REDACTED]. Even a [REDACTED] improvement in predicted human exposure from this change will still be well below that of the NOAEL exposure by a considerable margin, further confirming the starting dose of [REDACTED] K0706 for this first-in-

human study. Finally, the NOAEL established in the [REDACTED] studies support the planned repeat dosing of CML subjects in Part B.

In agreement with its *in vitro* profile, K0706 shows potent activity in its *in vivo* models based on BCR-ABL and good systemic availability in oral administration in [REDACTED].

Additionally, to the proposed starting dose of [REDACTED] may be modified based on the data obtained from Part A of the study. The data from Part A of the study will help to confirm the expected bioavailability of the K0706 capsule formulation and examine the dose relationship in K0706 exposure in a homogenous study population. The systemic exposure of K0706 in Part A will allow prediction of multiple dose exposure possible in Part B. This information will help define the range of doses in Part B that would be predicted to achieve efficacious K0706 concentrations.

The initial administered dose will be the dose from Part A SAD study where acceptable safety was observed [e.g., 2 or more subjects do not develop Grade 2 or higher AEs (AEs; in the same biologic system that are not clearly and incontrovertibly related to something other than the IMP) in [REDACTED] subject cohort, or no subject develops AE Grade 3 or higher (that is not clearly and incontrovertibly related to something other than the IMP)]. Projections from PK parameters in the various PK species suggest that a once daily dosing schedule should not lead to significant drug accumulation; for this reason once daily dosing will be planned for subjects receiving multiple dose administrations.

Rationale for the study in Patients

The study will be an open-label dose-escalation study in subjects with BCR-ABL-related malignancies (see inclusion criteria for details). It will involve multiple doses per subject and will be used to determine the MTD and to help define the RP2D appropriate for these patient populations. Additionally, the conduct of the study in subjects will allow for drug activity assessments not possible with healthy volunteers. As is consistent with Phase 1 dose escalation multi-dose first in man studies, subjects will be selected to be resistant or intolerant to the local Standard of Care Therapy for their disease. Despite country differences, it is expected that such Standard of Care therapy will include at least 1 line of treatment with a CML TKI. Subjects enrolled should be resistant or intolerant to at least 3 TKIs or are not eligible (e.g., due to comorbidities, hypersensitivity to excipients, outside of the US - lack of insurance coverage) for their local country's regulatory authority approved and medically appropriate TKIs (e.g., a TKI that is effective against mutations in the patient's tumor).

6.1.1 Risk Assessment

BCR-ABL TKIs such as imatinib mesylate, dasatinib, nilotinib, bosutinib and ponatinib are used in the treatment of Ph+ leukemias and a number of AEs have been noted with their clinical use. While some of the observed AEs are common between the BCR-ABL TKIs used and contribute as a class effect, specific adverse reactions are associated with the structure of the BCR-ABL TKI used. Since K0706 is being developed as a TKI for the treatment of Ph+ leukemias, AEs commonly observed with the approved BCR-ABL TKI class of drugs may be observed with the clinical use of K0706 as well. Additionally, long term toxicity data in [REDACTED] and data from Part B of the study did [REDACTED] indicate any [REDACTED] [REDACTED]

The following AEs have been reported during clinical studies and clinical use of BCR-ABL TKIs such as imatinib [REDACTED] dasatinib [REDACTED] nilotinib [REDACTED] ponatinib [REDACTED] and bosutinib [REDACTED]. Similar AEs could be associated with the use of K0706, see Appendix II (Section 13.2) and the IB for more details:

- Fluid retention: It is advised to monitor subjects for development of signs and symptoms of fluid retention.
- Myelosuppression: It is advised to monitor complete blood counts regularly.
- Cardiac arrhythmias: Subjects should be advised to report signs and symptoms of slow or rapid heart rate. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Caution is recommended when administering to subjects with hepatic impairment.
- Heart failure: Subjects should be monitored for signs or symptoms consistent with cardiac dysfunction and should be treated appropriately.
- Hepatotoxicity It is advised to monitor liver function tests regularly.
- Pancreatitis: Caution is recommended in subjects with a history of pancreatitis
- Hemorrhage: Caution is indicated in subjects requiring medications that inhibit platelet function or anticoagulants.
- Pregnancy: Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- Tumor lysis syndrome: Correction of clinically significant dehydration and treatment of high uric acid levels are recommended.
- Compromised wound healing and gastrointestinal perforation.

Other drug specific AEs observed with the use of BCR-ABL TKIs include, hepatic impairment, neuropathy, ocular toxicity, and vascular occlusion (arterial and venous) with

the use of ponatinib and renal toxicity with bosutinib use. Sudden deaths and electrolyte disturbances have been reported with the use of nilotinib.

From the data available with clinical use of K0706, the most frequently observed treatment emergent adverse effects in the study were from the following System Organ Classes:

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

Most drug related events were mild to moderate in intensity and resolved with or without treatment. These events are known with the use of TKIs and are expected for this class of drugs. For additional details, refer to IB.

6.1.2 Urgent safety measures

The Sponsor and Investigator should take appropriate urgent safety measures in order to protect the subjects of a clinical study against any immediate hazard to their health or safety. If such measures are taken the Sponsor shall (no later than 3 days from the date the measures are taken) give written notice to the licensing authority and the relevant Ethics Committee of the measures taken and the circumstances giving rise to those measures.

6.2 STUDY OBJECTIVES

6.2.1.1 Primary Objectives

The primary objectives of the study are to:

- To determine the MTD (or RP2D) of K0706 administered
- To evaluate the safety of K0706

6.2.1.2 Secondary objectives

The secondary objectives of the study are to:

- To evaluate the therapeutic activity of K0706
- To evaluate the PK of K0706 after multiple oral doses in subjects with the selected BCR-ABL-associated hematologic malignancies

6.2.1.3 Exploratory Objectives

The exploratory objectives of the study are to evaluate the genetic alterations that may correlate with K0706 resistance, such as:

- BCR-ABL mutation profile at therapy start (screening)
- BCR-ABL mutation profile at progression (should it occur)

6.3 INVESTIGATIONAL PLAN

6.3.1 Overall Study Design

The study will be an open-label, dose-ranging, single-agent, multicenter, multidose, dose escalation study initiated in subjects with Ph+CML (Ph+ CML include CML-CP, AP and BP [without the BCR-ABL T315I mutation]) and Ph+ ALL. Eligible subjects will be treated in [REDACTED] cycles of once-daily self-administered K0706. While K0706 should be preferably taken after [REDACTED], the subjects should be instructed to maintain [REDACTED] IMP dosing throughout the study.

To determine the MTD and/or the RP2D, the study will initiate with an accelerated titration dose-escalation design and transition to a 3+3 design when the first subject enrolled in the initial accelerated titration dose escalation cohort develops grade 2 or higher AE that is not clearly and incontrovertibly related to the underlying disease or concomitant medication.

The initial dose escalation cohorts can enroll at least 1 and up to 3 subject into each cohort. The subject enrolled into each cohort following the accelerated design of the initial escalation steps will receive the initial IMP administration, and continue to receive IMP at the same dose daily (unless [s]he qualifies for intra-subject escalation as described in Section 6.3.1.1. In cases where more than 1 subject have been entered in the accelerated titration component of the study, only the 1st subject will be evaluable unless the Sponsor and Investigator deem otherwise. If the first subject enrolled in this cohort does not experience a Grade 2 or higher AEs or DLTs during Cycle 1 of his/her study treatment

[REDACTED] the dose for the next subject(s) will be escalated to the next dose level. Enrollment into subsequent cohorts will proceed only after the current cohort has completed Cycle 1 of study treatment.

A subject administered a dose lower than the highest studied dose may have his/her dose increased up by one dose level at a time or to a dose that is 1 dose level below the highest studied dose, as per Investigator's discretion provided that the conditions stipulated in Section 6.3.1.1 are met.

In cases where more than one subject have been entered in the accelerated titration component of the study, only the 1st subject will be evaluable unless the Sponsor and Investigator deem otherwise. If this first subject enrolled in this cohort experiences a Grade 2 or higher AE that is not clearly and incontrovertibly related to the underlying disease or concomitant medications, then that cohort and all subsequent cohorts will follow the standard 3+3 design. All toxicities will be considered when making decisions regarding drug escalation increments or discontinuations, unless they are clearly and incontrovertibly related to the underlying disease or concomitant medications. When more than 1 subject is enrolled, enrollment may occur concurrently and the subjects may be administered their IMP concurrently.

For the cohorts where the 3+3 design applies, 3 subjects will be enrolled initially. If 2 of these subjects experience a Grade 2 or more toxicity (that is not clearly and incontrovertibly related to the underlying disease or concomitant medications), subsequent cohorts will be escalated according to smaller increments. Further, if there are no DLTs in the first 3 subjects, dose-escalation to the next higher dose level may proceed. If 1 of the 3 subjects experiences a DLT, that dose level will be expanded to 6 subjects (3 additional subjects will be enrolled). If 2 subjects at a given dose level experience a DLT, the MTD will have been exceeded. The next lower dose level will be expanded to 6 subjects, or if 6 subjects have already been enrolled and no more than 1 of the 6 subjects experienced a DLT, then this lower dose level will be considered the MTD.

Once the MTD or RP2D is established, the Sponsor and Principal Investigators may elect to add up to 12 additional subjects in each of the subgroups as expansion cohorts (i.e.: CML-CP, CML-AP, CML-BP, T315I CML-CP and Ph+ ALL) using the modified toxicity probability interval design starting at the MTD or RP2D for each subset of subjects. The T315I CML-CP cohort will be opened only when sufficient plasma levels found to be active preclinically in the T315I clone are achieved in the dose escalation cohorts. Until then Subjects with T315I mutations will not be enrolled in any part of the study.

Subject(s) in the subgroup expansion cohorts will start at MTD or RP2D achieved in the dose escalation cohorts. Initially, three subjects will be enrolled into each of the subgroup expansion cohort and monitored for DLTs. An internal Data Monitoring Committee (iDMC) will be convened after the 3 subjects have completed the DLT observation period. Stopping rules and subsequent dosing strategy will be made as per the algorithm described in the schematic for modified toxicity probability interval as depicted in Figure 6-2. The iDMC may recommend enrolling subsequent subjects at the same dose level if escalation criteria are met (e.g. DLTs in $\leq 1/3$ subjects) depending on emerging safety-efficacy profile. The second set of up to 9 subjects will be enrolled if stopping rule is not met after review of data from first 3 subjects. Separate MTD or RP2D may be identified for CML-CP, CML-AP, CML-BP, T315I CML-CP and Ph+ ALL.

The RP2D will be that dose level selected for further clinical evaluation; selection of the RP2D will be based on safety, tolerability, preliminary anticancer activity findings, and the observed trough blood level for K0706 relative to levels found to be active preclinically.

The decision to advance to the next dose level will only occur after careful evaluation of safety and tolerability data for a given dose level by the Sponsor and Principal Investigator after completion of Cycle 1; data from later cycles of treated subjects may be taken into consideration in this decision.

Additionally, an internal data monitoring committee consisting of members from the Sponsor, the investigative site, the CRO and an independent member will be formed to oversee the study. A formal charter will be generated that will describe the responsibilities of this group and submitted as an IND amendment prior to the initiation of Part B.

Details of the dose escalation process and doses to be administered are provided in Section 6.3.1.1.

A subject experiencing a DLT may continue therapy with a reduced dose of K0706. Subjects who experience a DLT and recover, may be treated (at the Investigator's discretion) at the next lower dose level until disease progression or other events requiring further dose reduction exist. For cohorts at Dose Level 2 or higher, a further dose reduction (i.e., up to 2 levels lower than their originally assigned dose) may be implemented in the case of a further DLT or other non-DLT events requiring a dose reduction, if and when the event leading to dose reduction returns to Grade 1 or lower in severity. Further dose reduction or delay or both may be implemented basis joint discussion between investigator and sponsor's medical monitor basis evaluation of subject's clinical condition. The reduced dose may be re-escalated to the original or higher dose (ie: dose for which safety has been established in the dose escalation cohort) at Investigator's discretion considering subject safety and response to the study drug and in consultation with Sponsor's medical monitor. Subjects experiencing a Grade 4 toxicity attributable to K0706 will undergo dose reduction and dose delays as per guidance provided in Section 6.4.2.1. [REDACTED]

The study will consist of a screening wherein all the required clinical and laboratory investigations to establish the eligibility of the patient for the trial is completed. Subject's disease diagnosis and status will be confirmed using the pathology reports available with the subject at the time of screening initiation. Only the latest pathology reports, subsequent to which there has been no change in therapy (with a potential to affect the disease course), will be considered for screening. [REDACTED]

Re-screening: [REDACTED]. Re-screening requests will be reviewed on case-by-case basis in consultation with the medical monitor of the CRO and/or Sponsor. Reasons that may qualify for a re-screening include 1) expiry of screening period due to personal issue or timing or prior withdrawal of consent by subject 2) stabilization or discontinuation of prohibited concomitant medication 3) medical condition that has now resolved. However, re-screening is not allowed if the previous

failure was because of eligibility criteria that are unlikely to change (example: h/o allergy to the excipients, significant drug abuse, involvement in planning of study, confirmed incorrect disease diagnosis or re-screening puts the subject's safety at risk). In case of re-screening, the subject will be assigned a different screening number.

Subjects will enter the study center [REDACTED] on Day 1 to receive the first administration of IMP and will complete the required assessments and sample collections ([REDACTED]). While K0706 should be preferably taken after [REDACTED], the subjects should maintain [REDACTED] IMP dosing in all the cycles. Subjects may be admitted a day prior to Cycle 1 Day 1 dosing and if required stay overnight at the study center on Cycle 1 Day 1, based on Investigator's discretion. Subjects will complete the assessments on Cycle 1 Day 2 and may remain in the study center overnight for observation, at the discretion of the Investigator. Subjects will return for follow-up assessments [REDACTED] in Cycle 1 on Days [REDACTED].

Cycle 2 will have similar [REDACTED] sample collections on Day 1, and subjects will be required to return to the study center on Days [REDACTED] for [REDACTED] samples and other follow-up assessments. From Cycle 3 onwards, subjects will only be required to return to the study center once every 3 [REDACTED].

Note: The last observation/evaluations for each cycle may coincide with the Day 1 of next cycle e.g., Cycle 6 Day [REDACTED] observation may coincide with Cycle 7 Day 1). [REDACTED] samples will be collected on the day of the study visit from Cycle 3 onwards.

Subjects will remain on study treatment for approximately 60 months (i.e.: 5 years from 1st K0706 dosing), or until intolerance, subject withdraws from the study, or progression of disease. Subjects who discontinue the study will be followed up for survival (survival assessment includes information about subject survival and other anticancer therapies) every 3 months after the IMP discontinuation till 60 months from their first dose of K0706 or until death, withdrawal of consent, or the end of the study, whichever comes first.

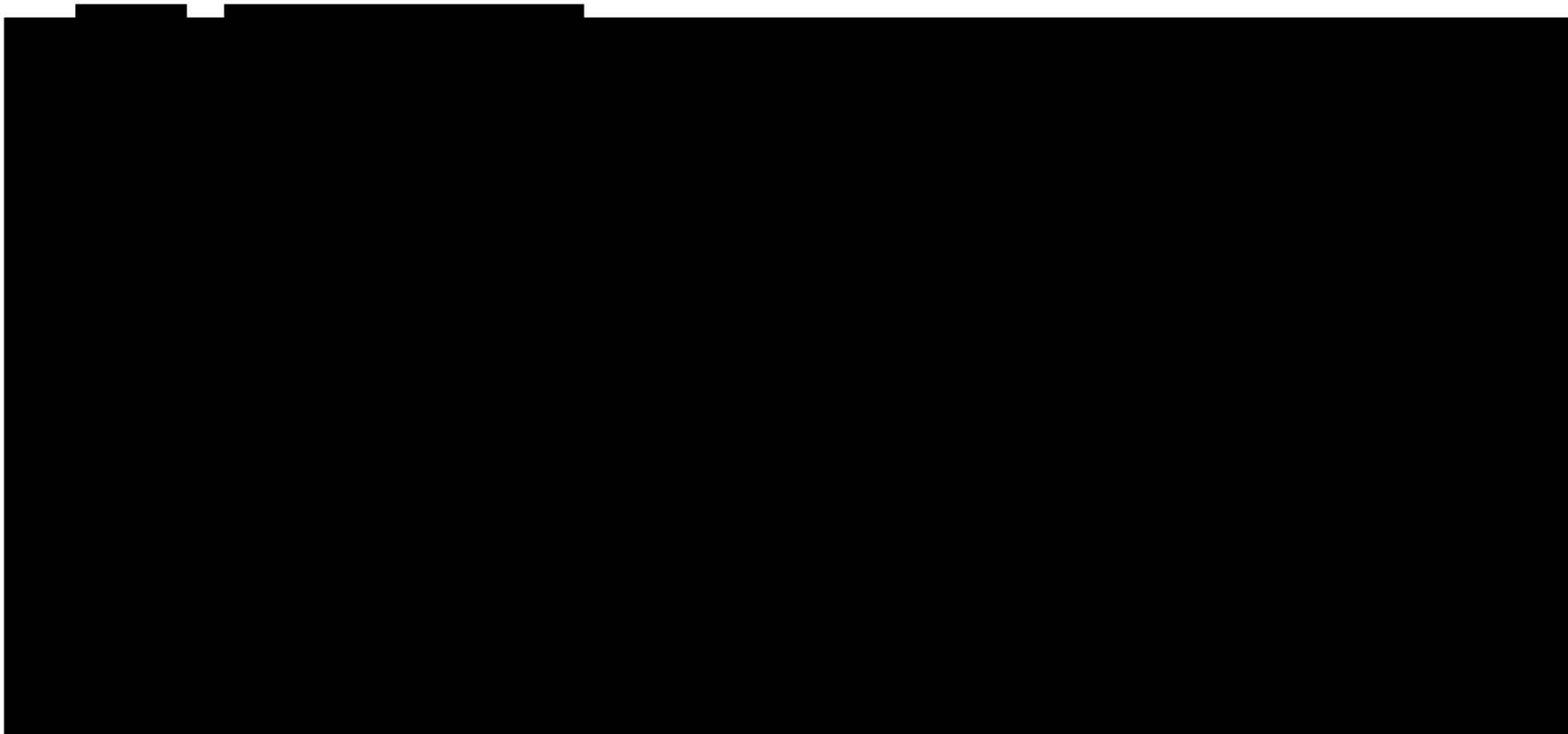
Treatment beyond 60 months will be considered, provided the Investigator considers that the subject is benefiting from K0706 therapy. Subjects who continue to receive K0706 beyond 60 months will be followed up for safety, survival and response assessments. Information about subject's survival and disease response will be collected at the follow up visits every 3 months in these subjects.

Medical Care of Subjects after the End of Treatment Visit:

After a subject has completed the study or has withdrawn early from the study, usual treatment (as per the local standards of care) may be administered, if required, in accordance with the study center's generally accepted medical practice and depending on the subject's individual medical needs. The Sponsor will not have any role to play in further treatment and the treatment regimen followed will be outside the purview of the study protocol. Information about subject's survival and anticancer therapies will be

collected every 3 months for approximately 60 months from the subject's first dose, by telephone contact, medical record review, and/or study center visits until death, withdrawal of consent, or the end of the study, whichever comes first. This information will be documented by the study center personnel in the subject's source documents and the electronic data capture system

Schematic of the design is presented in Figure 6-1 Schematic for the Study: PART B



- A. If medically warranted, subjects may be admitted to the study center overnight on Cycle 1 Day 1.
- B. The last observation and assessments for each cycle will coincide with the Day 1 of next cycle. The window period for Day 1 of every cycle in ± 3 days

[REDACTED]

[REDACTED]

6.3.1.1 Dose Escalation criteria

The decision to advance from one dose level to the next dose level will only occur after careful evaluation of all the available safety and tolerability data for a given dose level by the Sponsor and Principal Investigators after completion of Cycle 1; data from later cycles of treated subjects may be taken into consideration in this decision.

Progression to the next higher dose will only occur if the previous dose level was deemed to be safe and well tolerated by the Principal Investigator and the Sponsor.

An appropriate interval ([REDACTED]) will separate the investigation of dose levels to permit a timely review and evaluation of safety data prior to proceeding to the next higher dose level.

When it is not appropriate to escalate the dose then the same dose, a previous dose or an intermediate dose may be given following discussion between the Principal Investigators and Sponsor. Additional dose levels may also be investigated depending upon the results of the safety data from the previous dose levels and consideration of the preclinical toxicology data.

All data reviewed at the dose escalation meeting between the Principal Investigators and Sponsor ([REDACTED]) will be subjected to a quality review.

In cases where more than one subject have been entered in the accelerated titration component of the study, only the 1st subject will be evaluable unless the Sponsor and Investigator deem otherwise. If the first subject enrolled in this cohort does not experience Grade 2 or higher AEs or DLTs during Cycle 1 of his/her study treatment (i.e., [REDACTED])

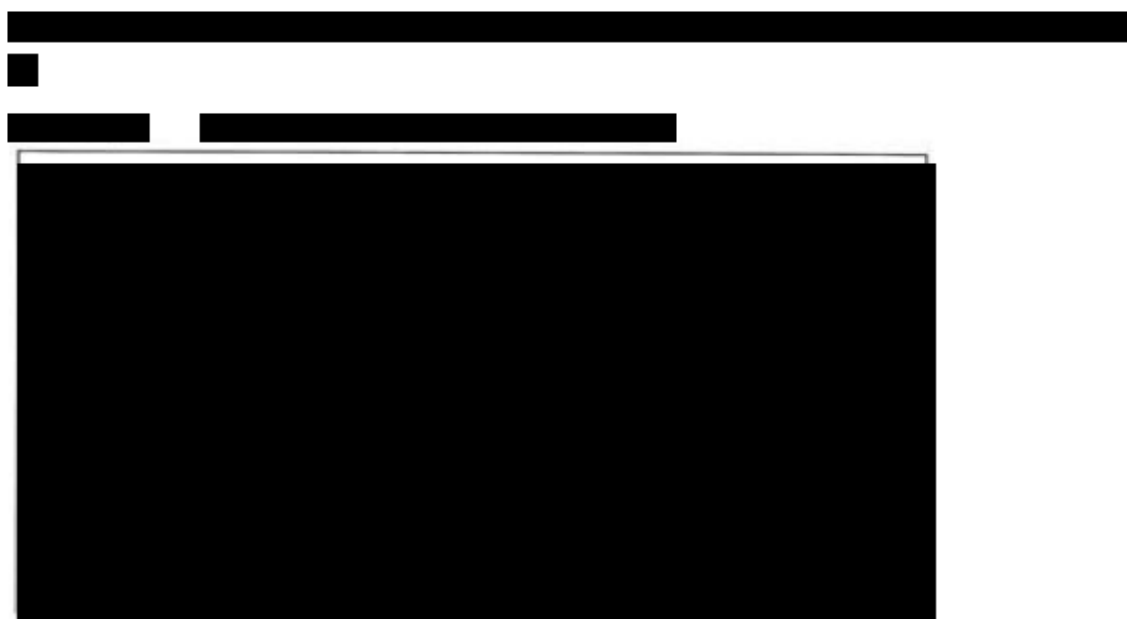
[REDACTED] the dose for the next subject(s) will be escalated to the next dose level. Enrollment into subsequent cohorts will proceed only after the current cohort has completed Cycle 1.

A subject administered a dose lower than the highest studied dose may have his/her dose increased up by one dose level at a time or to a dose that is 1 dose level below the highest studied dose, as per Investigator's discretion provided that:

1. The dose cohort to which the patient is being escalated has been completed (e.g., 1 cycle has been completed for all subjects).
2. The subject has not previously experienced a DLT.
3. The patient has no residual drug-related toxicity that is greater than grade 1.

Any results from intra-subject dose escalations will not affect inter-subject dose escalations unless the Investigator and Sponsor agree that intra-subject escalation information reasonably alters the potential benefit-risk ratio for subsequently treated subjects.

Dose escalations should occur at the beginning of a new cycle. Safety findings from intra-subject escalations will not be used for determination of the MTD of a regimen.



Abbreviations: D: Day, DLT: Dose limiting toxicity, MTD: Maximum tolerated dose.

In cases where more than 1 subject have been entered in the accelerated titration component of the study, only the 1st subject will be evaluable unless the Sponsor and Investigator deem otherwise. If this first subject enrolled experiences a Grade 2 or higher AE that is not clearly and incontrovertibly related to the underlying disease or concomitant medications, then that cohort and all subsequent cohorts will follow the standard 3+3 design. All toxicities will be considered when making decisions regarding drug escalation increments or discontinuations, unless they are clearly and incontrovertibly related to the underlying disease. When more than 1 subject is enrolled, enrollment may occur concurrently.

For the cohorts where the 3+3 design applies, 3 subjects will be enrolled initially. If there are no DLTs in the first 3 subjects, dose-escalation to the next higher dose level may proceed. If 1 of the 3 subjects experiences a DLT, that dose level will be expanded to 6 subjects (3 additional subjects will be enrolled). If 2 or more of 6 subjects at a given dose level experiences a DLT, the MTD will have been exceeded.

A DLT is defined as the occurrence of any of the following unless clearly and incontrovertibly related to the underlying disease. The hematological DLTs have been defined as per the Phase of CML:

- [REDACTED]
[REDACTED]
[REDACTED]
- Missed $\geq 25\%$ of doses over 28 days due to toxicity in Cycle 1
- Any grade of toxicity requiring dose reduction or discontinuation of IMP within the 28 day DLT assessment period [REDACTED]

Hematological DLT, as per the Phase of the Chronic Myeloid Leukemia:

- Hematological DLTs for subjects in CML-Chronic Phase
 [REDACTED] for ≥ 28 days off the study drug treatment or [REDACTED]
 [REDACTED] ≥ 7 days off the study drug (i.e.: after treatment interruption)
- Hematological DLTs for Subjects in CML-Accelerated Phase
 [REDACTED] for ≥ 28 days off the study drug treatment or [REDACTED]
 [REDACTED] ≥ 7 days off the study drug (i.e.: after treatment interruption) in the absence of features of accelerated phase (except cytogenetic changes) such as persistent increase in blasts or basophils
- Hematological DLTs for Subjects in CML-Blast Phase

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

Definition of the MTD: The MTD is defined as the dose that is 1 dose level lower than the dose at which a DLT is seen for [REDACTED] subjects administered the same dose of K0706 in Cycle 1 of therapy.

The MTD dose level will be expanded to [REDACTED] subjects, or if [REDACTED] subjects have already been enrolled and no more than [REDACTED] subjects experienced a DLT, then this lower dose level will be considered the MTD.

Subjects who experience a DLT and/or have a treatment delay may continue treatment in the absence of disease progression as long as the toxicity has recovered to the baseline value or lower.

A subject experiencing a DLT may continue therapy with a reduced dose of K0706. Subjects who experience a DLT and recover, may be treated (at the Investigator's discretion) at the next lower dose level until disease progression or other events requiring further dose reduction exist. For cohorts at Dose Level 2 or higher, a further dose reduction ([REDACTED]) may be implemented in the case of a further DLT or other non-DLT events requiring a dose reduction, if and when the event leading to dose reduction returns to Grade 1 or lower in severity. Further dose reduction or delay or both may be implemented basis joint discussion between Investigator and Sponsor's medical monitor basis evaluation of subject's clinical condition. The reduced dose may be re-escalated to the original or higher dose (i.e.: dose for which safety has been established in the dose escalation cohort) at Investigator's discretion considering subject safety and response to the study drug and in consultation with Sponsor's medical monitor. Subjects experiencing a Grade 4 toxicity attributable to K0706 will undergo dose reduction and dose delays as per guidance provided in Section 6.4.2.1. [REDACTED]
 [REDACTED].

Once [REDACTED] subjects experience a Grade [REDACTED] or [REDACTED] subject experiences Grade [REDACTED] toxicity (unless the AE is clearly and incontrovertibly related to underlying disease), further dose escalation steps will be reduced to [REDACTED] increments. The capsule composition of these doses will be assembled from the available capsule sizes and the selected dose will be rounded downwards rather than upwards to achieve a dose near the [REDACTED] increment. The capsules themselves will not be altered, only the combination of different capsules to be administered, [REDACTED]
 [REDACTED].

Definition of the RP2D: The RP2D will be the dose level selected for further evaluation; selection of the RP2D will be based on safety, tolerability, PD, preliminary anticancer activity findings, and the observed trough blood level for K0706 relative to levels found to be active preclinically.

6.3.1.2 Study Stopping Rules

The dose escalation in the study will be stopped when the MTD is reached or if continued evaluation of higher doses is not anticipated to add meaningful information for subsequent clinical development of the IMP for each planned cohorts in Part B or earlier if it is determined at any time that the risk benefit is unacceptable for any reason.

6.3.1.3 Discussion of Study Design

The study will be conducted in an open-label manner and all subjects will receive K0706. The rationale for the study and starting doses to be administered are presented in Section 6.1.

Appropriate safeguards for subject well-being and criteria for discontinuation of the K0706 in an individual subject and stopping rules are presented in Sections, 6.3.2.5, and 6.3.1.2 respectively.

An internal data monitoring committee consisting of members from the Sponsor, the investigative site, the CRO and an independent member will be formed to oversee the study. A formal charter will be generated that will describe the responsibilities of this group and submitted as an IND amendment prior to the initiation of Part B.

PK sampling and measurement of the drug concentrations will enable the assessment and comparison of the population PK profile of K0706. The duration of PK sampling has been chosen to sufficiently characterize the population PK of K0706.

In the study, due to the accelerated design, the cohort sizes will vary with [REDACTED] subjects being enrolled to each cohort. All subjects enrolled to the same cohort will receive the same dose level of K0706. Any specific subject will only be enrolled once, in a single cohort throughout the study. At least one and up to three subjects will be enrolled into each cohort following the accelerated design of the initial escalation steps. The subject(s) will receive the initial K0706 administration, and continue to receive K0706 at the same dose daily. This single dose level accelerated escalation will proceed to the next dose level unless there are Grade [REDACTED] or higher AEs or DLTs within the cohort's [REDACTED] observation period. In cases where more than 1 subject have been entered in the accelerated titration component of the study, only the 1st subject will be evaluable unless the Sponsor and Investigator deem otherwise. If the 1st enrolled subject experiences a Grade [REDACTED] or higher AE that is not clearly and incontrovertibly related to the underlying disease 2 or concomitant medications, additional subjects will be enrolled at that current dose. That cohort and all subsequent cohorts will follow the standard 3+3 design. All toxicities will be considered when making decisions regarding drug escalation increments or discontinuations, unless they are clearly and incontrovertibly related to the underlying disease. When more than 1 subject is enrolled, enrollment may occur concurrently and the subjects may be administered K0706 concurrently.

6.3.2 Study Population

Up to approximately [REDACTED] subjects will be enrolled. This number includes the dose-escalation cohorts and the sub-group expansion cohorts.

Up to approximately [REDACTED] subjects will be enrolled in the dose escalation phase. Up to approximately [REDACTED] subjects will be enrolled in the sub group expansion cohorts. In case the MTD is not defined within the predefined dose levels, more subjects may be enrolled.

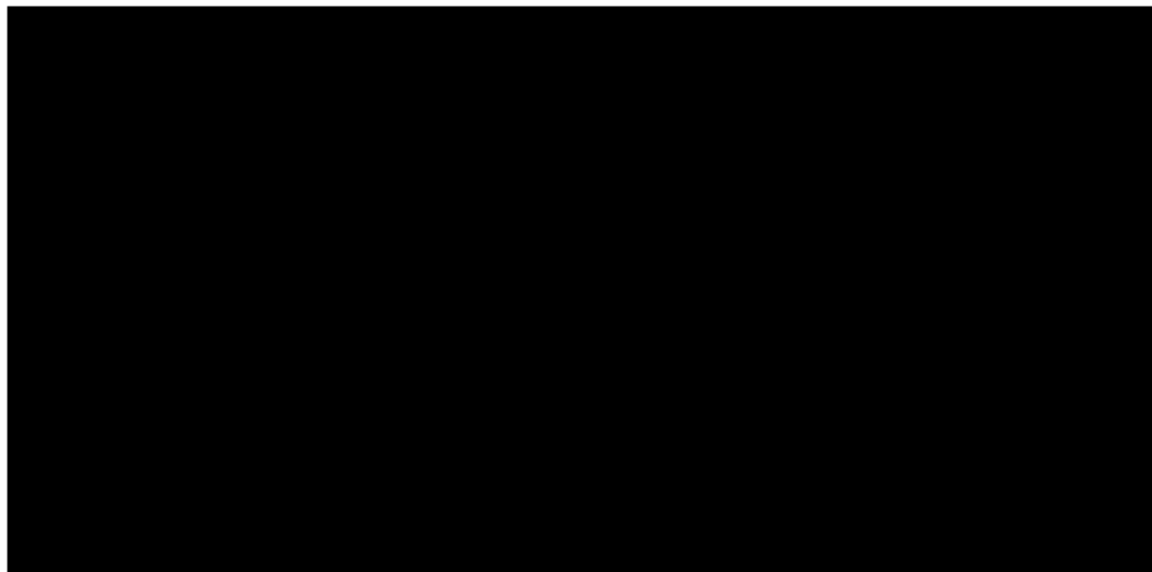
Subjects with Ph+ CML-CP, Ph+ CML-AP, Ph+ CML-BP or Ph+ ALL will be entered into the study provided that they satisfy the inclusion/exclusion criteria presented in Section 6.3.2.1.1 and 6.3.2.1.2.

6.3.2.1.1 Subject Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria:

1. Willing and able to give written/signed, and dated, informed consent (or by legally acceptable representative/impartial witness when applicable inclusion of subjects needing legally acceptable representative/impartial witness will be in compliance to the enrolling country's regulatory requirement) and is available for the entire study.
2. Willing and able to comply with the scheduled visits, treatment plan, laboratory testing, study procedures, and restrictions and be accessible for follow-up
3. Subjects diagnosed with Ph+ CML-CP, Ph+ CML-AP, Ph+ CML-BP or Ph+ ALL who are refractory or intolerant to at least 3 TKIs or are not eligible (e.g.: due to comorbidities, hypersensitivity to excipients, lack of insurance coverage) for their local country's regulatory approved and medically appropriate TKIs (e.g.: a TKI that is effective against mutations in the patient's tumor)
4. Male or female aged ≥ 18 years
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
6. [REDACTED]

| | |
|------------|------------|
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |



7. Subjects of childbearing potential must practice an medically acceptable method of birth control as judged by the Investigator:
- a. Medically acceptable methods of birth control include the use any of the effective birth control methods listed below –
 - i. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
 - ii. Progestogen-only hormonal contraception associated with inhibition of ovulation
 - iii. Placement of an IUD/ intra-uterine hormone releasing system. Consideration should be given to the type of device or system being used, as there are higher failure rates quoted for certain types, e.g., steel or copper wire
 - iv. intrauterine hormone-releasing system (IUS)
 - v. same sex partner, a vasectomized partner/bilateral tubal occlusion
 - b. The contraceptive should have been used continually within the past 3 months and the subject has to agree to continued use during the study and for 3 months after the last IMP administration.
 - c. To adopt another birth control method, or a double-barrier method which consists of a combination of any 2 of the following: diaphragm, cervical cap, condom, or a spermicide. The barrier method must be used in combination with another highly effective, non-barrier method (such as mentioned in Inclusion criteria # 7a) for at least 2 months prior to study entry and must continue to use contraception for the duration of the study and for 3 months after the last IMP administration.

- d. Subjects who are postmenopausal for at least 1 year based on history and Investigator's opinion or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy has been performed on the subject). For women < 45 years with menopausal symptoms, the menopause status to be reconfirmed by suitable laboratory tests including FSH level.
8. Male subjects enrolled in the study should not father a child and are advised to prevent passage of semen to their sexual partner during intercourse using an acceptable method as detailed in the Inclusion criteria # 7 and judged by the Investigator for the duration of the study and for 3 months after the last IMP administration
9. Female subjects of childbearing potential must have a negative pregnancy test (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin).
10. Female subjects must be non-lactating and non-breast-feeding

6.3.2.1.2 Subject Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Presence of T315I mutations
*(*Note: Enrollment of subjects bearing T315I mutation will be opened when sufficient plasma levels found to be active preclinically in the T315I clone are achieved)*
2. Any major surgery, as determined by the Investigator, within 4 weeks of IMP administration (Exceptions: Minor procedures such as bone marrow biopsy/aspiration, catheter placements and other procedures which in investigators' opinion do not compromise subject safety)
3. Inability to swallow oral medication
4. Inability to undergo venipuncture and/or tolerate venous access
5. Evidence of clinically significant organ dysfunction or any clinically relevant deviation from normal in physical examination, ECG findings, vital signs, or clinical laboratory test findings as per the Investigator's discretion.
6. Positive tests: urine pregnancy tests (if applicable), HIV
7. History of any relevant allergy/hypersensitivity (including known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the IMP or its excipients)
8. Known history of active hepatitis B or hepatitis C

9. Received any other investigational agent within 30 days or a washout of at least 5 half-lives, whichever is longer, of IMP administration
10. Use of concomitant medication that might influence the results of the study prior to IMP administration and/or anticipated need at any time during the study
11. Known or suspected history of significant drug abuse as judged by the Investigator
12. Known or suspected history of alcohol abuse or excessive intake of alcohol in the 12 months prior to study entry
13. Involvement in the planning and/or conduct of the study (applies to Sponsor, Contract Research Organizations, and study center staff, etc.)
14. [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
15. Malabsorption syndrome or other illness that could affect oral absorption of the IMP

- [REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]
 - [REDACTED]
[REDACTED]
[REDACTED]
 - [REDACTED]
[REDACTED]
 - [REDACTED]
[REDACTED]

17. Uncontrolled intercurrent illness including, but not limited to the following:
ongoing or active infection, uncontrolled seizure disorder, psychiatric or social
circumstances that would limit compliance with study requirements as per the
Investigator's discretion
18. Subjects who are eligible for potentially curative therapy that is available,
including hematopoietic stem cell transplant
19. Autologous or allogeneic stem cell transplant \leq 3 months prior to Screening; any
evidence of ongoing graft versus host disease (GVHD) or GVHD requiring
immunosuppressive therapy \leq 28 days prior to the first IMP administration visit
20. Another primary malignancy within the past 3 years or earlier (except for
adequately treated non-melanoma skin cancer or cervical cancer in situ)
21. Any condition or illness that, in the opinion of the Investigator, would
compromise subject safety or interfere with the evaluation of the safety of the
study drug
22. Intake of any restricted medications as described in the study restrictions (Section
6.4.6.1)
23. Any contraindications for repeated bone marrow sample collection
24. Active central nervous system (CNS) disease as evidenced by cytology or
pathology. In the absence of active CNS disease, lumbar puncture is not required.
History of CNS disease is not exclusionary if CNS disease has been cleared and
documented by negative lumbar puncture and other necessary procedures at
screening.

6.3.2.2 Classification of CML and Ph+ ALL subjects

Subjects will be classified as per the NCCN guidelines for Chronic Myeloid Leukaemia as follows:

Table 6-1 Classification of Subjects with CML

| CML Phase | Criteria |
|---------------|---|
| Chronic Phase | $< 15\%$ blasts in peripheral blood or bone marrow and $< 20\%$ basophils in peripheral blood and $< 30\%$ (blasts + promyelocytes) in peripheral blood or bone marrow and $> 100 \times 10^9$ platelets/L in peripheral blood |


| | |
|-------------------|---|
| | and No extra-medullary disease |
| Accelerated Phase | ≥ 15 - < 30 %blasts in peripheral blood or bone marrow or $\geq 20\%$ basophils in peripheral blood or bone marrow or $\geq 30\%$ (blasts + promyelocytes) in peripheral blood or bone marrow (but $< 30\%$ blasts) or $\leq 100 \times 10^9$ platelets/L in peripheral blood unrelated to therapy or Additional clonal cytogenetic abnormalities in Ph+ cells |
| Blast Crisis | ≥ 30 % blasts in peripheral blood, bone marrow or both or Extra-medullary disease |

Note: For subjects wherein rapid disease progression is observed (beyond the aforementioned criteria) and subject safety is a concern, the subject can be discontinued at Investigator's discretion in consultation with Sponsor or Sponsor nominated CRO's medical monitor.

For subjects to be classified as Ph+ ALL, the subject should have evidence of > 20 % blasts in the blood or bone marrow at the time of initial diagnosis and should not have had prior history of CML

6.3.2.3 Criteria for Disease Progression

Table 6-2 Criteria for disease progression of subjects enrolled into the study

| Disease status at enrolment | Disease progression criteria | Reference |
|-----------------------------|--|---|
| CML-CP | Progression to CML-AP or CML-BP at any time during the study Or WBC count that rises to $> 20.0 \times 10^9$ /L ($> 20,000/\text{mm}^3$) on two occasions at least 2 weeks apart (after first 4 weeks of K0706 therapy) in a subject Or Platelet count that rises to $> 600 \times 10^9$ /L ($> 600,000/\text{mm}^3$) on two occasions at least 2 weeks apart (after first 4 weeks of K0706 therapy) in a subject Or Loss of CHR (in the absence of a CyR) confirmed by complete blood counts done 4 weeks apart Or Loss of MCyR |  |

| | | |
|----------------------------|---|------------|
| | Or Death | |
| CML-AP | Development of BP Or Loss of previous major haematological response over a 2 week period Or No decrease from baseline levels in percentage blasts in peripheral blood or bone marrow on all assessments over a 4 week period (monitored at least every week) Or Death | [REDACTED] |
| CML-BP/ Ph+ ALL | Increasing blasts in peripheral blood or bone marrow over a 4 week period (monitored at least every week) Or For Ph + ALL, localization of disease at extra-medullary sites necessitating alternative therapy (example: Localization of ALL in breast tissue confirmed by histopathology or alternate methodology including clinical evidence) Or Death | [REDACTED] |

Note: For subjects wherein rapid disease progression is observed (beyond the aforementioned criteria) and subject safety is a concern, the subject can be discontinued at Investigator's discretion

6.3.2.4 Restrictions

The following restrictions will apply to all subjects during the study -

- Women and men must continue birth control for the duration of the study and at least 3 months after the last administration of IMP. See Section 6.3.2.4.2 for acceptable forms of contraception.

- Subjects should refrain from the use of concomitant medications that might reasonably influence the results of the study prior to K0706 administration and at any time during participation in the study. For restrictions regarding the allowed and disallowed medications, see Section 6.4.6.
- While K0706 should be preferably taken [REDACTED], the subjects should maintain approximately [REDACTED] IMP dosing throughout the study.

6.3.2.4.1 Avoidance of Pregnancy

Prior to study enrollment, women of childbearing potential (WOCBP) must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy.

Pregnancy should be avoided by either true abstinence or the use of 2 effective means of contraception (see Section 6.3.2.4.2) for the duration of the study and a total period of 3 months after the subject has taken the last administration of IMP.

Women of Childbearing Potential

Non-pregnant subjects and subjects of childbearing age must agree to use effective methods of contraception. All WOCBP must practice an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

All WOCBP must have a negative pregnancy test prior to first receiving IMP. If the pregnancy test is positive, the subject must not receive IMP.

In order to include WOCBP in any clinical study, certain precautions pertaining to pregnancy must be taken. These will include pregnancy testing at Screening and the EoT visit.

Female subjects who become pregnant during the study will be withdrawn. If a subject becomes pregnant during the study, the pregnancy will be recorded as a significant medical event and reported per the SAE reporting procedures.

Women of Non-Childbearing Potential

Female subjects of non-childbearing potential are defined as women who had a bilateral oophorectomy/hysterectomy or are postmenopausal, having been amenorrheic for at least 12 months with an appropriate clinical profile, e.g., appropriate age, history of vasomotor symptoms. For women < 45 years with menopausal symptoms, the menopause status to be reconfirmed by suitable laboratory tests including FSH level.

Male Subjects

Men enrolled on this study should understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control.

As there is no information for K0706 being secreted in the ejaculate, male subjects (including men who have had vasectomies) including whose partners are currently pregnant should use barrier method for the duration of the study and a total period of 3 months after the subject has taken the last administration of IMP. This is to ensure that the fetus is not exposed to the IMP in the ejaculate.

There is no information about effects that K0706 could have on the development of the fetus in humans; however, K0706 is a teratogen and induces fetal toxicity in toxicology studies. Therefore, it is important that the partners of male subjects do not become pregnant during the study and for a total period of 3 months after the male subject has received the last administration of IMP.

6.3.2.4.2 Acceptable Forms of Contraception

Highly effective methods of birth control are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. These include female sterilization (i.e., documented bilateral tubal ligation), hormonal methods of contraception (oral, implanted, injected, or transdermal) or an IUD in combination with a barrier method (condom, diaphragm). Individually, hormonal, barrier or IUD methods alone are not acceptable.

Acceptable forms of effective contraception are:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation
- Placement of an IUD/ intra-uterine hormone releasing system. Consideration should be given to the type of device or system being used, as there are higher failure rates quoted for certain types, e.g., steel or copper wire
- intrauterine hormone-releasing system (IUS)

The following should be noted:

- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection
- Spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone

Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject. For the female partners; bilateral tubal occlusion (with the appropriate post-tubectomy/tubal ligation documentation). History of bilateral oophorectomy or hysterectomy (with the appropriate documentation).

True abstinence: Refraining from heterosexual intercourse. The reliability of the sexual abstinence has to be evaluated in relation to the duration of the clinical trial and 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.

The acceptable method of contraception must be followed for at least 2 months prior to study entry and must continue to use contraception for the duration of the study and for 3 months after the IMP administration.

6.3.2.4.3 Time Period for the Collection of Pregnancy Information

All pregnancies in female subjects and the female partners of male subjects receiving at least 1 administration of K0706 will be recorded from the date of the first K0706 administration. Pregnancy in female subjects and the female partners of male subjects should be reported up to 3 months after the final IMP administration if the Investigator becomes aware of a pregnancy following the subject's last visit.

6.3.2.4.4 Follow-up in the Event of a Pregnancy

If a female subject, or the female partner of a male subject, who has received K0706 becomes pregnant the pregnancy will be recorded on the Pregnancy Reporting Form. The pregnancy will be communicated to all stakeholders as per the local regulations. The subject will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise.

Spontaneous miscarriage, maternal/neonatal complications, and congenital abnormalities will be reported as SAEs.

The follow-up period will be deemed to have ended when the health status of the child has been determined at birth.

6.3.2.5 Subject Withdrawals

The Investigator will make every reasonable attempt to have the subjects complete the study. However, a subject may withdraw from the study at any time without giving any reason. The Investigator will inform the Sponsor of the withdrawal of any subject.

A subject may be withdrawn in any of the following circumstances:

- Adverse events such as Grade 3 or 4 non-hematological toxicities [or hematological toxicities, clearly and incontrovertibly associated with use of

K0706 confirmed with bone marrow assessment to delineate disease involvement of the bone marrow] not optimally managed with dose delays and reductions, which in the opinion of the Investigator, can affect overall subject's safety or requires measures which would not allow the continued fulfillment of the protocol requirements and restrictions

- Occurrence of new mutations along with signs/symptoms or laboratory evidence of disease progression
- Non-compliance with study and follow-up procedures
- Entry in another therapeutic clinical trial or start of additional anti-cancer therapy
- Subjects who have missed K0706 intake for 2 consecutive weeks due to events associated with K0706 administration [REDACTED]
- Protocol violation
- Pregnancy
- Subject is lost to follow-up
- Subject withdrawal of consent
- Progression of disease
- Termination of the study by the Sponsor

The Investigator should as far as possible have the subjects who withdraw complete the assessments at the EoT visit (see Section 11.1). The EoT visit should be completed within 30 days or earlier after withdrawal of the subject. In cases of disease progression, necessitating initiation of an alternative anti-leukemic treatment, the EoT treatment can be completed at an earlier time point within the 30 days after withdrawal of the subject.

1) If EoT visit has occurred within 30 days and all EoT assessments have been completed, a separate 30 day safety follow-up should be completed: The decision of using either telephonic discussion/ site visit/medical record review for the 30 day safety follow up will be based upon investigator's assessment of the need basis subject's clinical history and clinical condition.

2) If EoT visit has occurred before 30 days and all EoT assessments have not been completed, a separate 30 day safety follow-up should be completed: In these cases: Assessments which have been missed on EoT visit, may be done at the 30 day safety follow-up visit. If based upon investigator's assessment of the subject's clinical history and clinical condition the recommendation is for using either telephonic discussion/medical record review instead of site visit for the 30 day safety, consultation with Sponsor's medical monitor should be sought for the missing EoT parameters.

3) If at EoT/30 day safety follow up visit there are any unresolved AEs/SAEs, they will be followed until resolution or until the event is stabilized or until it can be explained by another known cause (i.e. concurrent condition or medication) as per medical judgment of the investigator. The follow up methodology will be based on investigator's discretion and subject's clinical history and clinical condition. Any SAE reported by the patient after the completion of AE collection period and considered related to the study drug should also be reported by the investigator. Disease progression is not considered an AE in this study unless it leads to death or hospitalization in which case it should be reported as SAE.

Subjects who discontinue the study will be followed up for survival (survival assessment includes information about subject survival and anticancer therapies) every 3 months (± 2 weeks) after the IMP discontinuation till 60 months from their first dose of K0706 or until death, withdrawal of consent, or the end of the study, whichever comes first.

6.4 STUDY TREATMENT

6.4.1 Investigational Medicinal Product

All subjects will receive a continuous once daily oral administration of K0706 in a [REDACTED] cycle.

6.4.1.1 K0706

[REDACTED]. The details of K0706 are provided in Table 6-3.

Table 6-3 Details of K0706

| | |
|----------------|--|
| K0706 capsules | Description: [REDACTED] capsules [REDACTED] [REDACTED] [REDACTED] [REDACTED] |
|----------------|--|

See Section 6.4.2 for details on the doses to be administered in the study. Please see the IB for further information on K0706.

6.4.1.2 Placebo

No placebo will be administered.

6.4.1.3 Supply, Packaging and Labelling

The IMP will be supplied to the study centers by a Contract Research Organization appointed by the Sponsor.

A sufficient quantity of [REDACTED] capsules prepared for the human studies containing K0706 will be supplied to the study centers. The [REDACTED] formulation for K0706 will be manufactured by SPARC/SPARC approved vendor and stored in compliance with GMP conditions and labelled in accordance with local regulations.

Individual subject treatments will be dispensed by the study center pharmacist in appropriate containers with child-resistant twist-off caps. All clinical study material will be packaged and labelled to comply with applicable regulations. The IMP will be clearly labelled according to local requirements regarding use for clinical study investigation only and will be labelled with the IMP name, protocol number, Kit number, Lot number, expiry date, date dispensed, Subject number. Details may be added or deleted depending upon the local regulatory requirements in the participating countries. Separate documentation regarding the expiry or retest date will be made available.

Dispensing of the IMP to the subject and reconciliation of the returned IMP will be documented by the site staff. A technical agreement between the study center and the CRO will be in place to cover all pharmacy related activities, detailing roles and responsibilities prior to receipt of the IMPs at the study center.

6.4.1.4 Storage and Handling Procedures

The IMPs will be stored as below:

Store at room temperature [REDACTED] in a tightly closed container protected from light and moisture. Excursions are permitted to [REDACTED]

The storage area of the study centre, will be a secure, temperature controlled, and locked environment with restricted access.

6.4.1.5 Accountability

In accordance with GCP, the study center will account for all supplies of K0706. Details of receipt, storage, assembly, and return will be recorded.

All unused supplies of K0706 will either be destroyed by a designated vendor or will be returned to the study Sponsor at the end of the study in accordance with instructions by the Sponsor.

6.4.2 Dosage and Administration

K0706 capsules will be self-administered. The subject should be instructed about the following :

- While K0706 should be preferably taken [REDACTED], the subjects should maintain approximately [REDACTED] dosing throughout the study.

- The initial administered dose in Part B will be the dose from Part A Single ascending dose study where acceptable safety was observed (e.g., [REDACTED] subjects do not develop Grade [REDACTED] or higher AEs [AEs; in the same biologic system that are not clearly and incontrovertibly related to something other than the IMP]) in [REDACTED] subject cohort, or no subject develops AE Grade [REDACTED] or higher (that is not clearly and incontrovertibly related to something other than the IMP)]. Dose escalation in Part B will be dependent upon the total accumulated scientific information available in this study, and in the scientific literature, at any given time (when a decision to escalate, de-escalate, or continue must be made). This decision will incorporate the consensus opinion of the Part A investigator and the Sponsor. [REDACTED]

[REDACTED]

[REDACTED]

In the study, the subject will be required to return to the study center to receive their administration of K0706 for [REDACTED] Cycle 1. After administration of K0706 on [REDACTED] the subject will be dispensed with a sufficient amount of K0706 to last for the remainder of Cycle 1. From Cycle 2 onwards, a sufficient amount of K0706 to last until at least the subject's first scheduled visit of the next cycle will be dispensed to the subject on the first day of the cycle.

The subject will be required to bring the dispensed K0706 to the study center at each visit and the Investigator is to confirm the number of capsules taken and remaining before returning K0706 to the subject.

[REDACTED]

| [REDACTED] | [REDACTED] | [REDACTED] |
|------------|------------|------------|
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |

The subject will also be supplied with a diary card on which is to be recorded the date and time K0706 is taken, meals timings before and after IP consumption as well as any other medications that the subject may have taken during the course of the day (along with the reason for taking the medication). The diary will be dispensed on visits in which there is an onsite visit and the subject will be required to bring the diary to each visit to the study center where the Investigator will review the diary and record the details into the eCRF.

The date and time when K0706 is administered will be documented in the subject's diary card and eCRF. Additionally, the following should be recorded-

1. Was the IMP taken [REDACTED] (yes/no [REDACTED])
 [REDACTED]

2. [REDACTED]

6.4.2.1 Dose Delays and Reductions

Dose delays or reductions or both may be implemented for subjects who experience adverse drug reactions with K0706. Subjects who experience a DLT and recover, may be treated (at the Investigator's discretion) at the next lower dose level until disease progression. [REDACTED]

[REDACTED]. Further dose reduction or delay or both may be implemented basis joint discussion between investigator and sponsor's medical monitor basis evaluation of subject's clinical condition. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

6.4.2.1.1 Dose Delay or Reduction for [REDACTED] adverse events attributable to K0706

Dose delay or reduction or both may not be implemented for [REDACTED] toxicities which are attributable to the K0706 if these toxicities can be managed with supportive care or are non-interfering with normal daily activities of the patient. If the [REDACTED] toxicities are intolerable either due to clinical symptoms or due to interference with daily activities and are not controlled by optimal supportive care, the subject may be managed by holding the K0706 [REDACTED] (dose delay) to allow for amelioration or resolution of the event to Grade [REDACTED] or baseline. [REDACTED]

[REDACTED].

Subsequent study drug administration may be the next lower dose level as per Section 6.4.2.1. Occurrence of aforesaid event will qualify as a DLT.

6.4.2.1.2 Dose Delay or Reduction for [REDACTED] toxicities/adverse events attributed to K0706

Dose delay or reduction or both may be implemented for [REDACTED] toxicities which are attributable to K0706. In the event of a grade [REDACTED] AE, attributed to K0706, the subject may be managed by either dose reduction to one level lower dose as per the dose

escalation scheme. K0706 administration at the reduced dose level may be delayed for up to [REDACTED] to allow the event leading to dose reduction to ameliorate \leq Grade [REDACTED] or baseline or resolution. [REDACTED]

[REDACTED] Further dose reduction or delay or both may be implemented basis joint discussion between investigator and sponsor's medical monitor basis evaluation of subject's clinical condition. If required consultation with iDMC will be undertaken on decision making. [REDACTED]

6.4.2.2 Management of Missed Doses

Subjects who miss their scheduled dose of study drug should be instructed to not make up for the missed doses. If the patient forgets to take his/ her daily dose, then he/ she should take it within 6 hours after the missed dosing time. If more than 6 hours have passed, then that dose should be omitted and the patient should continue treatment with the next scheduled dose. The missed doses should be recorded in an appropriate source document and the CRF (Example: Patient diary, study drug administration record).

6.4.3 Treatment Strategy

The staff at the study centers are all responsible for the ongoing safety and well-being of the subjects while they are resident in the study centers.

It is expected that study centers participating in this study will have a working system/method (such as, but not limited to, a paging system, emergency phone lines, etc.) to alert the staff to any area in the unit where a subject may need medical attention. In the case of an emergency, cardiac resuscitation trolleys will be available in the main ward areas of the study center. These trolleys contain drugs, equipment for airway insertion, circulation lines, defibrillation etc., together with oxygen cylinders and portable suction machines. Physicians will be present for dosing and close observation over the first 8-12 hours after IMP administration.

If necessary the clinical staff can contact further on-call physicians or public emergencies services, including an ambulance, in the event of a serious medical event. The site should be equipped for anticipated emergencies in this patient population.

6.4.4 Monitoring of Study Drug Administration

Subjects will be provided a Patient diary or its equivalent. Subjects will be provided training on use of the subject diary by the site. Subjects who miss their doses will be instructed to not make up for the missing doses within 6 hours. Subjects will be instructed to enter all the missed doses in the subject diary. Whenever possible, subjects should take the study drug under observation during scheduled study visits to the clinic. A scanned copy of the subject diary should be maintained by the CRO and sent across to the sponsor at the end of every cycle for the first 3 cycles and thereafter at the end of every 3 cycles (i.e. end of Cycle 6, 9, 12 and beyond).

6.4.5 Warnings and Precautions

Although the effects of similar TKIs are known, all effects of K0706 cannot be reliably predicted. The preclinical data suggest an acceptable safety margin. See the IB for details on events that could be expected.

Use of anti-clotting agents

Serious bleeding events, including fatalities have occurred in patients treated with TKIs like imatinib mesylate, dasatinib and ponatinib. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Cerebral hemorrhage and gastrointestinal hemorrhage were the most commonly reported serious bleeding events. Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia. Caution is indicated in patients requiring medications that inhibit platelet function or anticoagulants.

Use of Cytochrome inhibitors

Tyrosine kinase inhibitors should be used with caution when concurrently used with moderate and strong CYP3A inhibitors (such as clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit juice) and moderate or strong CYP3A inducers (such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort). Sensitive substrates of CYP2C8 with a narrow therapeutic index should be avoided or used with caution in this trial (Refer to section 6.4.6.1).

6.4.6 Prior and Concomitant Medication

See section 6.4.6.1 for precautions with regards to the use of anti-clotting agents and CYP inhibitors.

Medications other than those specifically excluded in this study may be administered for management of symptoms associated with administration of K0706 as needed. These medications include analgesics, anti-nausea medications, antihistamine, anti-anxiety medications, and medication for pain management (narcotic agents are included).

In addition, the following treatments must not be administered during the study:
Immunotherapy, immunosuppressive drugs and Growth factors (other than mentioned in section 6.4.6.1)

| Country | Year | Value |
|---------------|------|-------|
| United States | 2010 | 100 |
| United States | 2011 | 100 |
| United States | 2012 | 100 |
| United States | 2013 | 100 |
| United States | 2014 | 100 |
| United States | 2015 | 100 |
| United States | 2016 | 100 |
| United States | 2017 | 100 |
| United States | 2018 | 100 |
| United States | 2019 | 100 |
| United States | 2020 | 100 |
| United States | 2021 | 100 |
| United States | 2022 | 100 |
| United States | 2023 | 100 |
| United States | 2024 | 100 |
| United States | 2025 | 100 |
| United States | 2026 | 100 |
| United States | 2027 | 100 |
| United States | 2028 | 100 |
| United States | 2029 | 100 |
| United States | 2030 | 100 |
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| United States | 2092 | 100 |
| United States | 2093 | 100 |
| United States | 2094 | 100 |
| United States | 2095 | 100 |
| United States | 2096 | 100 |
| United States | 2097 | 100 |
| United States | 2098 | 100 |
| United States | 2099 | 100 |
| United States | 2100 | 100 |

[illegible]

The following nondrug therapies must not be undertaken or administered during the study (or within 4 weeks before the start of IMP administration):

- Major surgery (excluding diagnostic biopsy)
- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin)
- Subjects should not abuse alcohol or other drugs during the study

6.4.6.2 Permitted medications

- Short-term administration of systemic steroids (that is, for allergic reactions or management of immune- or infusion-related AEs) is allowed.
- Granulocyte-Colony stimulating factor, Erythropoietin and darbepoetin-alpha as exceptions may be prescribed at the discretion of the Investigator.
- Transfusion of blood and related products such as platelet or red blood cells may be prescribed at the discretion of the Investigator.
- Where appropriate, hydroxyurea or anagrelide are permitted during the first cycle of K0706 administration. Concomitant use must be discontinued by the end of the third week of K0706 in subjects with AP, BP, Ph+ALL and by the end of the first cycle in all subjects, and is thereafter prohibited.

6.4.7 Method of Assigning Subjects to Treatment Groups

At Screening, potential study subjects will be assigned a Screening number. Following confirmation of eligibility, before IMP administration, subjects will be assigned a subject number in the order in which they are enrolled in the study.

6.4.8 Randomization Procedures

Subjects in the study will not be randomized. All eligible subjects will be assigned to treatment with K0706. Subjects will be sequentially assigned to a specific cohort as they are enrolled in the study.

6.4.9 Maintenance of Randomization Codes

Not applicable.

6.4.10 Blinding

The study will be open-label.

6.5 STUDY PROCEDURES

The Schedule of Assessments to be performed of the study is presented in Section 11.1. The approximate volume of blood to be collected from each subject in a given cohort is provided in the table below.

[REDACTED]

[REDACTED]

Should multiple assessments overlap, the PK samples are to be collected as close to the prescribed PK sample collection time point as possible. Whenever a PK sample and other

assessments are to be obtained simultaneously the sequence should be: scheduled 12-lead ECG, vital signs measurements, PK blood samples (to be performed at the precise protocol scheduled time), and then any other scheduled or unscheduled measurements at that time point.

6.5.1 Pharmacokinetic Assessments

Blood samples [REDACTED] will be collected at specified time points to determine plasma concentrations of K0706. Blood sample collection times are included in the schedule of assessments (see Section 11.1).

Individual venipunctures for each time point may be performed or an indwelling catheter may be used. [REDACTED]

[REDACTED] Heparin may not be used to flush the catheter. The exact date/time of the blood sample collection will be recorded in the subject's eCRF.

[REDACTED]. Details of sample collection procedures, sample preparation (if applicable), sample collection tube, sample labelling, sample storage and sample shipment will be described in a separate Laboratory Manual.

Bio analysis

Determination of the plasma concentrations of K0706 will be performed using a validated method.

The details on the analytical methods used will be described in a separate bioanalytical report.

6.5.2 Efficacy Assessments

Detailed collection tubes, sample processing, label, storage, and shipment information will be described in the Laboratory Manual. The details of the analytical methods used will be described in a separate bioanalytical report. Biological samples collected during the conduct of the study will be retained for a period of up to [REDACTED] after study closure, not exceeding the time strictly necessary for the fulfillment of the purposes of the study; samples could be stored for a longer duration as per applicable regulatory requirements.

Serum, blood, and bone marrow-based samples will be collected at specified time points to assess the efficacy endpoints of interest, see section 6.5 for more details. Sample collection times are included in the schedule of assessments (see Section 11.1).

6.5.2.1 Mutation Profiling

Mutation testing for BCR-ABL sequencing will be performed on [REDACTED] samples.

The BCR-ABL mutation profiling may be done [REDACTED] as a primary assay. [REDACTED].
Sample logistics and the location of testing will be detailed in the Laboratory Manual.

6.5.2.2 Cytogenetic Response

Bone marrow aspirate samples will be sent for review of cytogenetics [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].

For subjects who demonstrate complete cytogenetic response on two repeated assessments, bone marrow aspirate samples may be collected at [REDACTED] intervals thereafter.

Standard cytogenetic methods will be used to determine the presence of the Ph+ and its presence (percentage) in the bone marrow. [REDACTED]
[REDACTED] Bone marrow cytogenetics should be performed within 7 days of scheduled date irrespective of missed doses or disease or dose associated AEs.

Peripheral blood cells [REDACTED] used for conventional cytogenetic response monitoring.
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

- [REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]

Sample logistics and the location of testing will be detailed in the Laboratory Manual.

6.5.2.3 Major Molecular Response

Molecular response monitoring (MMR) using PCR for BCR-ABL copy number will be performed on the collected blood samples and will be assessed [REDACTED] as per the schedule of assessments.

A molecular response is defined as a negative PCR or other negative molecular test. A PCR test is defined as a very sensitive test which can be used to detect the presence of very low levels of specific genetic material (DNA). It is used to detect, and sometimes to quantify, BCR-ABL in bone marrow cells of patients with CML. The most sensitive PCR tests can detect as few as one in 100,000 copy number/ mL.

[REDACTED]

Sample logistics and the location of testing will be detailed in the Laboratory Manual.

6.5.2.4 Hematologic Response

A hematological response is a normalization of the blood counts, particularly WBC counts. This is the first noticeable indicator that treatment is beginning to work, though not necessarily in the bone marrow. The response can be a partial hematological response (reduction in WBC, but not down to normal range) or CHR.

The CHR will be evaluated [REDACTED] utilizing local laboratory results.

A CHR is usually anticipated within the first 3 months of treatment, however, some subjects may take longer to achieve this level. The majority of subjects easily achieve this milestone on or before the 3 month mark.

Refer to Appendix I and Operations Manual for the definitions of CHR and MaHR.

Sample logistics and the location of testing will be detailed in the Operational Manual.

6.5.3 Safety Assessments

6.5.3.1 Adverse Events

The safety and tolerability of subjects will be assessed by the incidence of treatment emergent AEs, study drug discontinuation information, laboratory test results, vital signs, ECGs and physical examination findings.

Definitions:

Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, be related to study procedures or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Untoward medical experience occurring during medication-free pre-treatment periods does not meet the above-mentioned definition of an AE. Nevertheless, they have to be documented in the same way as AE. Each subject will be queried generally for the occurrence of adverse experiences prior to study drug administration and throughout the subject's participation in the study. During and following a subject's participation in this study, the Investigator has to ensure that adequate medical care is provided to a subject for any AE, including clinically significant laboratory values.

The investigator will document all AEs in the subject's source document and eCRF. All entries should contain an event term, date of onset, date of resolution, severity, action taken, outcome, relationship to study drug, and a seriousness assessment.

Adverse Drug Reaction

An adverse drug reaction is an "untoward and unintended response to an IMP related to any dose administered".

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse drug reactions. The expression of "reasonable causal relationship" means to convey in general that there are facts or arguments which suggest a causal relationship.

Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that, at any dose

- Results in death
- Is life-threatening

- Requires in-subject hospitalization or prolongation of existing hospitalization*
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important Medical Event or requires medical intervention to prevent one of the outcomes listed above.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (eg, sudden death, unexplained death), the death per se might then be reported as an SAE.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which, hypothetically, might have caused death if it were more severe.

*A planned hospitalization for pre-existing condition/s, or a procedure required by the Clinical Investigation Plan; minor procedures without a serious deterioration in subject's health (e.g.: catheter or feeding tube placements etc.) or hospitalization clearly unassociated with an AE (e.g., social hospitalization, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not to be considered as SAEs. Any Hospitalization due to social and logistic reason will not be considered as SAE. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Treatment-Emergent Adverse Event

TEAEs are defined as any AE occurring or worsening on or after the first dose of IMP.

Unexpected Adverse Event

Any AE that is not identified in nature, severity, frequency or outcome in IB will be considered as unexpected. The IB version effective at the time of onset of the event will be used for assessment of expectedness of SAE. [Note: The effective date of an IB version is referring to the last RA approval date of the IB version in EU countries.] Additionally, the Principal Investigator will evaluate all AEs as follows:

Seriousness: whether or not the AE is fatal or life threatening, persistent or permanently disabling, requires or prolongs inpatient hospitalization, is a congenital anomaly or an important medical event.

Action taken with study drug: Action taken is categorized as "none", "study drug discontinued/withdrawn", "study drug discontinued temporarily and restarted", "dose modified", or "not applicable".

Event Outcome: Event outcome, or time last follow-up is recorded is categorized as “Fatal”, “Resolved”, “Resolved with sequelae”, “Resolving”, “Not Resolved”, “Unknown”.

Any AE that is not identified in nature, severity, frequency or outcome in IB will be considered as unexpected. The IB version effective at the time of onset of the event will be used for assessment of expectedness of SAE. [Note: The effective date of an IB version is referring to the last RA approval date of the IB version in EU countries.]

Categorization of Adverse Events

The grading scales found in NCI CTCAE v4.03 will be utilized for all AEs with an assigned CTCAE grading. For those AEs without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (<http://evs.nci.nih.gov/ftp1/CTCAE/About.html>).

If a particular AE’s intensity is not specifically graded by the guidance document, the Investigator is to use the general NCI CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are as follows:

Intensity, to be graded as:

| Degree | Description |
|------------------|--|
| Mild | Awareness of signs and symptoms; easily tolerated |
| Moderate | Discomfort sufficient to interfere, but not prevent daily activity |
| Severe | Unable to carry out usual activity |
| Life threatening | Life-threatening consequences; urgent intervention indicated. |
| Death | Death related to AE. |

Relationship to study drug, to be graded as:

| TERM | DEFINITION | CLARIFICATION |
|-----------|--|---|
| Unrelated | Those AEs which, after careful consideration, are clearly due to extraneous causes (medical history, demography details, disease, environment, etc.) | |
| Unlikely | A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, | 1. It does not follow a reasonable temporal sequence (Improbable temporal relationship) from administration of the drug. 2. It could also be explained by patient's concurrent disease, environmental factors, medical history and |

| TERM | DEFINITION | CLARIFICATION |
|-----------|--|--|
| | and in which other drugs, chemicals or underlying disease provide plausible explanations. | other concomitant drugs or chemicals including food-drug interactions |
| Possibly | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. | <ol style="list-style-type: none"> 1. It follows a reasonable temporal sequence from administration of the drug. 2. It could also be explained by patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals (including food-drug interactions). 3. There is no information or uncertainty with regard to what has happened after stopping the drug. |
| Probably | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition. | <ol style="list-style-type: none"> 1. It follows a reasonable temporal sequence from administration of the drug. 2. It could not be readily explained (unlikely) by the patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions. 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. 4. No rechallenge information is available or possible. |
| Certainly | A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary. | <ol style="list-style-type: none"> 1. It follows a plausible time sequence to drug intake, this means that there is a positive argument in sufficient detail to support the view that the drug is causally involved, pharmacologically or pathologically e.g. pharmacokinetics and type of reaction. 2. It could not be explained by patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions (i.e. no alternative causes). 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. 4. It is an objective and specific medical disorder or a recognized pharmacological phenomenon for instance 'grey baby syndrome' and chloramphenicol or anaphylaxis immediately after the administration of a drug that had been given previously. <i>This means that any other event is automatically excluded and can never qualify for 'Certain' (even in the case of a positive rechallenge observation).</i> 5. It reappears on readministration of the drug (only if ethically correct i.e. in case of non-serious, and easily treatable AEs). |

Assessment of Expectedness

The IB version effective at the time of onset of the event will be used for assessment of expectedness of SAE. [Note: The effective date of an IB version is referring to the last RA approval date of the IB version in EU countries.]

Additional guidance on the AE/SAE reporting

For AEs:

- AE reporting period for safety surveillance begins after subject is randomized into the study and receives at least 1 dose of IMP for treatment emergent adverse events (TEAEs) and continues until 30 days from end of treatment visit. Any AE which occurs 30 days after end of treatment visit or last dose of IMP will be reported if it is considered related to IMP/study procedure by the investigator.
- All physical examination (PE), medical history, and laboratory findings considered to be clinically significant and baseline events occurring post-consent, but prior to receiving the first dose of study medication will be classified and graded according to CTCAE nomenclature but will not be considered AEs and entered in subject's medical history.
- All study procedure related events occurring post consent and prior to first IMP administration will be recorded as Non Treatment Emergent Adverse Events (Non TEAEs).
- Disease progression as defined in Section 6.3.2.3 or as per clinical judgement of Investigator is not considered as an adverse event in the study, unless it leads to hospitalization or death in which case it should be reported as SAE. Subjects with disease progression should be discontinued from the study and their EOT visit be performed at the earliest.

For SAEs:

- SAE reporting period for safety surveillance begins after the subject consents for the study and continues until 30 days from end of treatment visit or last dose of IMP will be reported if it is considered related to IMP/study procedure by the investigator.
- All SAEs occurring prior to receiving the first dose of study drug will be recorded as Non TEAEs. Site as well as Sponsor/Sponsor's designee will comply with any additional reporting requirements of the EC/IRB and applicable local regulations.
- All deaths occurring in the study will be reported as SAEs to the Sponsor. Site as well as Sponsor/Sponsor's designee will comply with any additional reporting requirements of the EC/IRB and applicable local regulations.

Follow up of unresolved AEs: Any AE/SAE unresolved at end of study visit will be followed until resolution or until the event is stabilized as per medical judgement of the investigator.

Events Not to Be Considered as AEs/SAEs

Medical, baseline, pre-dosing conditions present at the initial study visit (ie: screening visits) that do not worsen in severity or frequency during the study, are defined as Baseline Medical Conditions and are not to be considered AEs.

For criteria pertaining to disease progression please refer to guidance in the aforementioned text on Additional guidance on AE/SAE reporting.

Suspected Unexpected Serious Adverse Reactions and Unexpected Adverse Reactions

Any suspected adverse reaction that is serious, unexpected, and considered to be related to drug exposure is defined as a SUSAR.

6.5.3.2 Reporting of Serious Adverse Events

All SAEs must be reported according to ICH GCP or local regulations, applying the regulation with the stricter requirements. The report will contain as much available information concerning the SAE to enable the Sponsor's safety physician/CRO to file a report, which satisfies regulatory reporting requirements. The SAE report will be notified by Investigator within 24-hours of his/ her awareness to the Sponsor's safety physician/CRO. These timelines apply to initial reports of SAEs and to all follow-up reports.

All AEs/SAEs will be recorded on the AE Report Form and SAE report form in the eCRF and source documents.

The following minimum information must be included in the SAE form:

- Name, address and telephone number of the reporting Investigator
- IP details
- Subject identification number, initials, sex and date of birth
- Description of the SAE, measures taken and outcome

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor's safety physician/CRO may have on the SAE. This is necessary to ensure

prompt assessment of the event by the Sponsor's safety physician to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

The contact details of Sponsor's safety physician are as follows:

Safety Physician

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

Follow-up Any unresolved AE/SAE will be followed up till resolution/stabilization or as per medical judgement of the investigator. The Investigator should take all appropriate measures to ensure the safety of the subjects, including referral to a specialist if indicated.

6.5.3.3 Pregnancy

A pregnancy test will be performed at screening and at visits specified in the protocol. Females of childbearing potential must not be pregnant or lactating (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin). Females of childbearing potential must agree to the use of a reliable method of contraception as described in Inclusion Criteria of this protocol and throughout the study. Subjects with a positive test at screening or during the study period will be excluded from study. Similarly, male subjects enrolled to the study will be instructed not father a child and avoid passage of semen to their partner by using an acceptable contraceptive method as discussed by the investigator during the enrolment to the study. However, if a female subject becomes pregnant during the study, the pregnancy will be recorded as a significant medical event and reported per SAE reporting procedure and the subject will be withdrawn from the study immediately. Similarly, if a female partner of a male subject becomes pregnant during the study, the medical event will be recorded appropriately. The 'pregnancy reporting form' will be completed and submitted to Sponsor. The pregnancy shall be followed every three months till its outcome and up to one month post-delivery to assess the functional status of the child. If any SAE occurs during pregnancy than it will be reported using SAE forms as per timelines defined in section above. Any congenital abnormalities or birth defects in newborn will be followed three months post-delivery.

6.5.4 Clinical Laboratory Safety Tests

Sample collection times are included in the schedule of assessments (see Section 11.1).

Clinical Laboratory tests including hematology, coagulation, clinical chemistry, and urinalysis will be performed. The details of the tests to be performed will be provided separately in the Operation's Manual. Other laboratory tests to be performed are shown below. Testing for Human immunodeficiency virus I and II will be done in serological examinations.

Additional and repeat testing may be performed at the discretion of the Investigator.

Unless otherwise specified in the Operation's Manual, the safety laboratory tests will be performed by the study center's local laboratory. Details of all methodology and reference ranges are provided in the Laboratory manual and Trial Master File.

The clinical laboratory test results will be reviewed for potential clinical significance by the Investigator. If the Investigator determines a laboratory value to be outside the normal laboratory range of the local testing laboratory and clinically significant, it should be considered an AE (and should be documented as such); however, if the laboratory value abnormality is consistent with a current diagnosis, it may be documented accordingly.

Urine pregnancy tests will be performed at the time points stipulated in the schedule of assessments (see Section 11.1).

See Section 6.5.6.4 for details on cardiac troponin I assessments to be performed separately from the laboratory tests listed above.

6.5.5 Clinical Safety Assessments

Assessment times are included in the schedule of assessments (see Section 11.1)

6.5.5.1 Vital Signs

Vital signs (including blood pressure [systolic and diastolic], pulse rate, respiratory rate, and temperature) will be measured in a supine position after the subject has rested comfortably for at least 5 minutes using an automated instrument.

Additional vital signs measurements may be performed for the safety of the subjects. The vital signs measurement results will be reported in the subject's eCRF.

If clinically significant findings, as determined by the Investigator, occur in any of the vital signs measurements, that measurement will be repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

6.5.5.2 12-Lead Electrocardiogram

A computerized 12-lead ECG (single replicate) will be performed with the subject in a supine position after the subject has rested comfortably for at least 10 minutes. The 12-lead ECG will be performed at Screening, Cycle 1 Day 1 and Day of Subject Discharge from the study Centre. [REDACTED]

[REDACTED] At investigator's discretion and/or availability of new information from the study more frequent ECG monitoring may be performed if clinically indicated. [REDACTED]

The Investigator, or a designee, will report whether the ECG is normal or abnormal and if the result is considered clinically significant or not. All clinically significant ECG abnormalities occurring during the study should be documented as AEs.

Standard ECG parameters, including heart rate, QRS, PR interval, RR interval, QT interval, and the QTc using Fridericia's formula will be measured. The ECGs will be read by the Investigator, or a designee, to assess any abnormalities.

6.5.5.3 Medical, Surgical, and Medication History

A complete medical history will include evaluation (past or present) of the following: general, head and neck, eyes, ears, nose throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, gynecological/urogenital, musculoskeletal/extremities, skin, neurological/psychiatric, endocrine/metabolic, hematologic/lymphatic, allergies/drug sensitivities, past surgeries, substance abuse or any other diseases or disorders.

Any surgical as well as medication use history is to be recorded as well, including the time and type of the surgery received or medication taken.

6.5.5.4 Physical Examination

Physical examinations will be performed and any changes compared to the Screening assessment will be recorded as AEs.

The physical examinations will be performed by a physician and will include the examination of the following: general appearance, weight and height (at Screening), abdomen; head and neck; eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, neurological/psychiatric.

Additional examinations may be performed as part of the physical examination at Investigator's discretion for any AE related physical examinations if found necessary in the clinical judgment of the Investigator.

6.5.6 Other Assessments

Assessment times are included in the schedule of assessments (see Section 11.1).

6.5.6.1 Demographic and Other Baseline Characteristics

Demographic data (including date of birth, age, race, ethnicity, gender, and menopausal status) will be recorded at Screening.

All subjects will be asked about their disease history and significant medical history (including drug history, any surgical history, and family history).

6.5.6.2 Eastern Cooperative Oncology Group Performance Status

ECOG status will be ascertained by investigator /designee at screening and subsequent visits as noted in the schedule of assessments and at survival follow-up.

6.5.6.3 Tumor Response Assessment

A variety of tests are used to diagnose, determine disease phase, and monitor CML for example:

1. Complete blood count with differential for hematological response assessments.
2. Bone marrow aspiration for cytogenetic assessments.
3. Bone marrow biopsy will be used only in cases wherein the bone marrow aspiration was unsuccessful because the marrow is too fibrous to permit aspiration through the bone marrow biopsy needle.
4. Florescence in situ hybridization will be utilized for detection of minimum residual disease or in cases wherein enough sample was not available to conduct karyotyping

Serum, blood, and bone marrow-based samples will be collected at specified time points.

6.5.6.4 Cardiac Troponin

A cardiac troponin I assay will be performed separately from the laboratory assessments (see Section 6.5.4) by the local laboratory and will be reported together with normal ranges. However, the sample collection will be included with the biochemistry sample collection.

6.6 DATA COLLECTION

A Code of Federal Regulations Title 21 Part 11-compliant EDC system will be used for this study. The eCRFs will be produced for each subject. The majority of study data collected will be either directly entered by the study center staff or directly captured from devices onto the eCRF. Data will be available for Sponsor review via predefined reports

extracted from the database at agreed intervals. The eCRFs must be kept in order and up-to-date so that they reflect the latest observations on the enrolled subjects.

When direct data entry onto the eCRF is inappropriate or impractical data will be collected on paper source documents and subsequently transcribed, where necessary, onto the eCRFs by the study center staff. All source documents will be retained. Photocopies of completed source documents will be provided only if essential (i.e., for regulatory purposes) at the request of the Sponsor.

Safety laboratory data are managed and stored within the appropriate system and only the date and time of sampling will be recorded in the eCRF. Safety laboratory data will be integrated with the consolidated clinical data before database lock.

The informed consent will be kept with a copy of the completed source documents in the appropriate file folder provided, or a note to indicate where the records can be located. All records should be kept in conformance to applicable national laws and regulations.

Validity and consistency of data will be checked by employing pre-programmed data validation rules that will be applied to the data extracted from the EDC system during the course of the study. The data management team will raise queries in the EDC system to resolve discrepancies. The Investigator must verify that all data entries in the eCRFs are accurate and correct. After completion of the study and when all collected data is validated, the database will be locked, pursuant to the prior approval by the Sponsor. Final data will be extracted from the EDC and delivered to the Sponsor in form of SAS® datasets. A portable document format copy of the eCRF will be produced for each study subject and included in the final delivery.

All eCRF entries, corrections, and alterations must be made by the Investigator or other, authorized, study center staff and only by individuals who have received training on the EDC system. Study center staff may be allowed access to the system only after the relevant training is completed. Training must be documented and a log of all EDC users and their rights within the system be maintained.

Adverse events will be coded using the current MedDRA dictionary; concomitant medications will be coded using World Health Organization's Drug Dictionary.

The EDC system will keep track of all data entry, alterations and query resolution in an audit trail. The audit trail will form an integral part of the database and will be archived alongside with the data.

6.7 EVALUATION OF STUDY DATA

6.7.1 Evaluation of Pharmacokinetic Parameters

Pharmacokinetic analysis will be performed [REDACTED]. The actual elapsed time from dose will be used in the final PK parameter calculations. Data handling, analysis procedures and data reporting will be detailed in the SAP.

Where possible, the following plasma PK parameters will be determined for K0706:

For Day 1 of Cycle 1 and Cycle 2

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Other parameters may be added as appropriate. The final PK parameters reported will be detailed in the SAP plan.

6.7.2 Evaluation of Efficacy

Efficacy will be determined by analysis of peripheral blood and bone marrow. Automated complete blood counts, differential counts (may include manual confirmation of abnormalities), physical examination, bone marrow differential, [REDACTED]

[REDACTED]

[REDACTED] will be used to determine the response to treatment. Cytogenetic, molecular, and hematologic response will be estimated for all subjects. The timing of these assessments will be according to the schedule of assessments, Section 11.1.

[REDACTED]

[REDACTED]

Automated complete blood counts and differential counts (with manual confirmation of abnormalities), physical examination, bone marrow differential, [REDACTED] will be used to determine response to treatment. CHR will be evaluated by peripheral blood utilizing local laboratory results. The local laboratory reference ranges will be included in the EDC. The local laboratory may be requested to perform manual confirmation of abnormalities using peripheral blood smears. In this case at least 3 separate smears prepared from the same sample should be read before reporting the results.

Bone marrow samples (i.e.: Bone marrow aspirates) will be evaluated for review of cytogenetics and [REDACTED]
 [REDACTED]
 [REDACTED]

Please see the Laboratory Manual for processing and shipping of samples.

Bone marrow aspirates obtained as part of standard of care prior to signing of ICF can be used at Screening as long as it was collected within [REDACTED] days of randomization and there has been no change in therapy for Part B of the study. Bone marrow aspirates will be performed as part of screening for Part C of the study. If bone marrow aspirates at screening yield an invalid result, the bone marrow aspiration will be repeated to have evaluable result prior to study drug administration on Cycle 1 Day1. Subject will be dosed upon confirmation of valid bone marrow evaluation outcome. In case of a repeat in bone marrow, screening period will be extended.

Standard cytogenetics will be used to determine the presence of the Ph+ and its presence (percentage) in the bone marrow aspirates. The Investigator must ensure that the pathology laboratory and/or pathologist performing the cytogenetic and florescence in situ hybridization analysis is blinded to treatment information and is trained in performing the procedure under appropriate aseptic conditions. Documentation of subject's treatment information cannot be contained in any request forms or directives for sample processing.
 [REDACTED]
 [REDACTED]
 [REDACTED]

Bone marrow cell differential will also be used to determine the blast and immature myeloid counts and cellularity if required.

Physical examination will be used to assess hepatic and spleen involvement.

To understand the exploratory objectives:

In Part B and Part C of the study, serum, blood, and bone marrow-based samples will be collected at specified time points to determine the following:

- BCR-ABL mutation profile at screening versus patient response
- BCR-ABL mutation profile at progression (should it occur)

Samples for BCR-ABL mutation profiles will be performed during Screening and at progression if observed. Additional efficacy parameters may be evaluated and will be detailed in the statistical analysis plan.

6.7.3 Evaluation of Safety

The safety and tolerability profile of K0706 in subjects treated on this study will be assessed by physical examination, AEs, vital signs (including blood pressure [systolic and diastolic], pulse rate, respiratory rate, and temperature), ECG, and clinical laboratory tests (including hematology, coagulation, cardiac troponin, clinical chemistry, and urinalysis). The timing of these assessments will be according to the schedule of assessments, Section 11.1.

Adverse events will be assessed based on the NCI CTCAE v4.03 and categorized as SAEs or AEs. The relationship of AEs to K0706 will be assessed by the Investigator per the protocol-defined criteria for attribution assessment.

Subject performance status will be assessed using the ECOG performance status scale.

Subjects who discontinue the study will be followed up for survival (survival assessment includes information about subject survival and anticancer therapies) every 3 months (\pm 2 weeks) after the IMP discontinuation till 60 months from their first dose of K0706 or until death, withdrawal of consent, or the end of the study, whichever comes first.

6.8 STATISTICAL METHODS

In general, descriptive summaries will be presented for the safety and efficacy variables collected. Continuous variables will be summarized [REDACTED]

[REDACTED]. Categorical variables will be summarized [REDACTED]

[REDACTED].

Adverse events will be coded using MedDRA and will be summarized by System Organ Class and Preferred Term. In addition, summaries of AEs by severity and relationship to K0706 will be presented.

Formal testing of treatment effects will not be performed. However, where appropriate, some measures will be summarized by both point estimates and estimation of 95%

confidence intervals. More detailed information about estimation of treatment effects, summarization of data, graphical representations, and analysis conventions will be provided in the SAP.

6.8.1 Primary and Secondary Target Variables

Primary Endpoints:

The primary endpoint will be:

- The MTD/RP2D as determined by the frequency of DLTs

The safety endpoint will be:

- AEs assessed based on the NCI CTCAE v4.03, ECOG performance status, vital signs, ECG, clinical laboratory values, and physical examination

Secondary Endpoints:

The secondary efficacy endpoint will be:

- Anti-leukemic response assessment following the hematological, cytogenetic and molecular assessments.

The PK endpoints will be:

- [REDACTED]
[REDACTED]
[REDACTED]

Exploratory Endpoints:

The exploratory pharmacogenomics endpoint will be:

- The BCR-ABL mutation profile at baseline and at disease progression (should it occur)

6.8.2 Sample Size Determination

The number of subjects to be enrolled in the study is dependent on the dose escalation scheme. The study design is an accelerated titration dose escalation design which will progress to a standard 3+3 design [REDACTED] with occurrence of a Grade [REDACTED] or higher AE that is not clearly and incontrovertibly related to the underlying disease or concomitant medications in any dose escalation cohort and with the sample size being dependent on the study results. However, the maximum number of subjects to be enrolled will not exceed [REDACTED] subjects in the dose escalation scheme. Further, for each subgroup of cohorts as defined in the protocol (Ph + CML include CML-CP, CML-AP, and CML-BP [without the BCR-ABL T315I mutation until sufficient plasma levels found to be active preclinically

in the T315I clone are achieved)) and Ph+ ALL will additionally enroll [REDACTED] subjects each. For the subgroups, initially [REDACTED] subjects will be enrolled and basis iDMC recommendation subsequent subjects may be enrolled at the same dose level if escalation criteria are met ([REDACTED]) depending on emerging safety-efficacy profile.

6.8.3 Subject Population for Analyses

6.8.3.1 Safety Analysis Set

The safety analysis set will include all subjects who receive at least 1 administration of IMP.

6.8.3.2 Efficacy analysis set

Dose escalation cohorts and dose expansion cohorts:

The efficacy analysis set will include all the subjects who have had at least one post-treatment efficacy assessment when on K0706 dosing.

6.8.3.3 Pharmacokinetic Analysis Set

The PK analysis set will include all subjects who receive at least 1 dose of K0706 and have at least 1 measured K0706 plasma concentration at a scheduled PK time point postdose with no important protocol deviations, violations, or events thought to significantly affect the PK of the drug.

6.8.4 Pharmacokinetic Analysis

6.8.4.1 Statistical Analysis of Pharmacokinetics

Plasma concentrations and PK parameters for K0706 will be listed and summarized [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Additionally, mean concentration profiles by dose cohort and cycle will be illustrated.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Any additional PK evaluations or illustrations will be described in the SAP.

6.8.5 Efficacy Analysis

The efficacy analysis will be performed separately per dose escalation cohort. For Part B dose expansion cohorts, the efficacy analysis will be performed separately per disease cohort.

6.8.6 Subject Disposition

The number of Subjects enrolled in Part B will be summarized separately. For Part B, subjects will be summarized by treatment/dose level/cohort/ disease sub-set (CML-CP, CML-AP, CML-BP, and Ph+ ALL).

6.8.7 Exploratory Analysis

Continuous PD endpoints will be summarized by dose cohort and/or disease subsets or disease cohorts and scheduled visit by descriptive statistics (n, mean, standard deviation, minimum, median, and maximum). Categorical endpoints will be summarized by proportion in each category by dose cohort and scheduled visit.

Any additional PD evaluations will be described in the SAP.

6.8.8 Safety Data Analysis

Individual and summary blood pressures, heart rate, ECG parameters and clinical laboratory data will be presented in tabular form with N, mean, median, standard deviation and range (minimum and maximum) as appropriate. The data will be summarized by dose cohort and scheduled visit. Unscheduled data will not be included in the summary tables, but will be included in the listings.

For the laboratory safety data, out of range values will be flagged in the data listings and a list of clinically significantly abnormal values will be presented.

Adverse events will be tabulated and summarized according to the current version of MedDRA. AEs will be summarized according to dose cohort.

6.9 STUDY REPORT: PART B

A clinical study report, compliant with the requirements of ICH E3, will be prepared by IQVIA.

7 PART C

7.1 RATIONALE

Rationale for the dose and treatment regimen in patients:

Rationale for K0706 dose:

The study aims at evaluating efficacy outcomes at the RP2D. An integrated dose-response and exposure-response analyses and an evaluation of accumulated clinical pharmacokinetic, safety and efficacy data as well as nonclinical pharmacology data was performed to arrive at the RP2D.

RP2D for K0706 was established [REDACTED].

RP2D dose was selected on the basis of correlation of K0706 plasma concentrations at the dose levels evaluated in Part B with K0706 concentrations required to inhibit *in vitro* proliferation of Ba/F3 cells expressing p210 BCR-ABL native and mutant kinases. Early efficacy and safety data obtained from Parts A and B was also correlated with the aforementioned to conclude on the RP2D.

[REDACTED]

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

K0706 is [REDACTED] in all species, independent of concentration. The [REDACTED] fraction of K0706 is proposed to contribute to *in vivo* efficacy. Minimum efficacious target plasma concentration in clinical setting thus requires adjustment for the functional effects of protein binding *in vivo*. [REDACTED]

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

An overview of the overall safety data indicates that there is [REDACTED] dose response in the incidence or nature of Treatment Emergent Adverse Events (TEAEs). [REDACTED]

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

Early anti-leukemic activity, (i.e.: major hematological response and cytogenetic response) is observed across K0706 doses from [REDACTED] in subjects refractory and/or intolerant ≥ 3 TKI therapies. [REDACTED] clear dose-response relationship is observed in terms of efficacy, due to underlying disease heterogeneity (i.e.: presence of mutations, clonal evolutions), limited number of subjects, intra-patient escalation and inherent heterogeneity of the enrolled subjects (i.e.: differences in the prior TKI therapies received). In this setting, treatment at an adequate dose and exposure is essential for achievement and durability of clinical response, keeping in mind the proposed Phase II disease population of those subjects who have failed ≥ 3 prior TKI therapies have poor overall survival and quick disease progression.

RP2D at [REDACTED] was concluded based on safety, tolerability, preliminary anticancer activity findings, [REDACTED]

[REDACTED]

Rationale for dose schedule

The study will involve daily oral dosing per subject at the recommended phase 2 dose (RP2D) of [REDACTED] cycles. Dosing schedule has been established in [REDACTED]

cycles in Part B of the study. The [REDACTED] cycles have been well tolerated and associated with anti-leukemic activity and disease response. Daily dosing contributes to maintenance of required K0706 plasma trough levels required for anti-proliferative activity associated with disease control. On the basis of the aforementioned, eligible subjects will be treated in [REDACTED] cycles with once daily dosing [REDACTED] of K0706.

While K0706 should be preferably taken [REDACTED], the subjects will be instructed to maintain approximately [REDACTED] IMP dosing throughout the study.

Rationale for Subjects with Previous Treatment

Subjects enrolled should be resistant or intolerant to at least 3 TKIs one of which includes ponatinib.

The *in vitro* growth inhibitory activity of K0706 on BCR-ABL positive and BCR-ABL negative cells is comparable to other approved TKIs (imatinib, nilotinib, dasatinib, and ponatinib), thus it is likely that there will be benefit similar to existing approved agents. Early anti-leukemic activity observed in subjects failing ≥ 3 TKIs in Part B of the study likewise suggests that there may be benefit similar to existing approved agents in the aforementioned disease setting with K0706.

Currently, there are no existing licensed TKI therapy for a patient who has failed 3 TKIs including ponatinib. The probability of the patients responding to any other existing approved TKI after failing on 3 TKIs including ponatinib is negligible.

7.1.1 Risk Assessment

BCR-ABL TKIs such as imatinib mesylate, dasatinib, nilotinib, bosutinib and ponatinib are used in the treatment of Ph+ leukemias and a number of AEs have been noted with their clinical use. While some of the observed AEs are common between the BCR-ABL TKIs used and contribute as a class effect, specific adverse reactions are associated with the structure of the BCR-ABL TKI used. Since K0706 is being developed as a TKI for the treatment of Ph+ leukemias, AEs commonly observed with the approved BCR-ABL TKI class of drugs may be observed with the clinical use of K0706 as well. Additionally, long term toxicity data in [REDACTED] and data from Part B of the study [REDACTED] indicate [REDACTED] new safety signal.

The following AEs have been reported during clinical studies and clinical use of BCR-ABL TKIs such as imatinib [REDACTED] dasatinib [REDACTED] nilotinib [REDACTED] ponatinib [REDACTED] and bosutinib [REDACTED]. Similar AEs could be associated with the use of K0706, see the Appendix II (Section 13.2) and the IB for more details:

- **Fluid retention:** It is advised to monitor subjects for development of signs and symptoms of fluid retention.
- **Myelosuppression:** It is advised to monitor complete blood counts regularly.
- **Cardiac arrhythmias:** Subjects should be advised to report signs and symptoms of slow or rapid heart rate. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Caution is recommended when administering to subjects with hepatic impairment.
- **Heart failure:** Subjects should be monitored for signs or symptoms consistent with cardiac dysfunction and should be treated appropriately.
- **Hepatotoxicity:** It is advised to monitor liver function tests regularly.
- **Pancreatitis:** Caution is recommended in subjects with a history of pancreatitis
- **Hemorrhage:** Caution is indicated in subjects requiring medications that inhibit platelet function or anticoagulants.
- **Pregnancy:** Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- **Tumor lysis syndrome:** Correction of clinically significant dehydration and treatment of high uric acid levels are recommended.
- **Compromised wound healing and gastrointestinal perforation.**

Other drug specific AEs observed with the use of BCR-ABL TKIs include, neuropathy, ocular toxicity, and vascular occlusion (arterial and venous) with the use of ponatinib and renal toxicity with use of bosutinib. Sudden deaths and electrolyte disturbances have been reported with the use of nilotinib.

From the data available with clinical use of K0706, the most frequently observed treatment emergent adverse effects in the study were from the following System Organ Classes: [REDACTED]

[REDACTED] Most drug related events were mild to moderate in intensity and resolved with or without treatment. These events are known with the use of TKIs and are expected for this class of drugs. For additional details, refer to IB.

7.1.2 Urgent safety measures

The Sponsor and Investigator should take appropriate urgent safety measures in order to protect the subjects of a clinical study against any immediate hazard to their health or

safety. If such measures are taken the Sponsor shall (no later than 3 days from the date the measures are taken) give written notice to the licensing authority and the relevant Ethics Committee of the measures taken and the circumstances giving rise to those measures.

7.2 STUDY OBJECTIVES

7.2.1 Primary Objectives

- To evaluate the anti-leukemic efficacy of K0706 in subjects with CML-CP by cytogenetic outcomes and in subjects with AP and BP by hematologic outcomes who have failed ≥ 3 TKIs one of which includes ponatinib.

7.2.2 Secondary Objectives

To evaluate

- Anti-leukemic efficacy of K0706 by molecular outcomes
- Anti-leukemic efficacy of K0706 by hematological outcomes in CML-CP
- Anti-leukemic efficacy of K0706 by cytogenetic outcomes in CML-AP and BP
- Time to first hematologic response
- Duration of response
- Progression free survival (PFS) and Overall survival (OS).
- Population PK of K0706.
- Safety of K0706 in the dosed subjects.

7.2.3 Exploratory Objectives

- To evaluate the genetic alterations that may correlate with K0706 resistance, such as:
 - BCR-ABL mutation profile at screening
 - BCR-ABL mutation profile at progression (should it occur).

7.3 INVESTIGATIONAL PLAN

7.3.1 Overall Study Design

The study will be a multicenter open-label study of oral K0706 in subjects with Ph+ CML (CP, AP, BP) who have documented resistance or intolerance to ≥ 3 prior TKIs one of which includes ponatinib. Subjects will be grouped in the following cohorts. (Subjects with Ph+ ALL will not be included the study.)

| Cohort A | Cohort B | Cohort C |
|--|--|-------------------------------------|
| Ph+ CML: Chronic Phase (CP) cohort | Ph+ CML: Accelerated Phase (AP) cohort | Ph+ CML: Blast Phase (BP) cohort |

Note: The number of subjects contributed by a site should not exceed approximately 20% of total study population as far as possible unless approved by the Sponsor.

Each of the three cohorts represent distinct patient populations and will be evaluated separately for efficacy and safety. The cohorts can be considered as 3 separate studies enrolled through this single protocol, hence no adjustments for multiplicity are planned. Eligible subjects will be treated in [REDACTED] cycles using once-daily, oral self-administered [REDACTED] K0706 and will be evaluated for K0706 anti-CML activity (hematological, cytogenetic and molecular response). Subjects enrolled in Part C [REDACTED] will remain in the study, but will not be considered for the statistical analysis for Part C. Intra patient dose escalation is permitted only for Part C subjects enrolled at [REDACTED]. Patients enrolled in Part C at [REDACTED] can be escalated upto [REDACTED] based on investigator's assessment of subject's tolerability and response.

Adverse events (AEs) will be assessed throughout the study until 30 days after discontinuation of the study drug. AEs will be graded as per National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. AEs will be followed to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause (i.e. concurrent condition or medication) and clinical judgment of the investigator indicates that further evaluation is not warranted. Disease progression will not be captured as an AE in this study unless it leads to death or hospitalization in which case it should be reported as SAE.

The study will consist of screening wherein all the required clinical and laboratory investigations to establish the eligibility of the patient for the trial is completed. Subject's disease diagnosis and status will be confirmed using the pathology reports available with the subject at the time of screening initiation. Only the latest pathology reports, subsequent to which there has been no change in therapy (with a potential to affect the disease course), will be considered for screening. Screening must be performed within [REDACTED] prior to first dose of K0706 (i.e.: Cycle 1 Day 1). The screening must be performed within [REDACTED] prior to the first dose of the study drug (i.e.: Cycle 1 Day 1) unless extension of screening period is granted by the CRO/sponsor medical monitor after an evaluation of the impact of the extended period on assessment of efficacy and safety. Subjects shall be dosed only after the eligibility is confirmed by CRO and/or sponsor MM.

During screening bone marrow aspiration and blood draws will be performed for bone marrow cytogenetics and BCR-ABL mutational and transcript analysis to re-confirm the disease status of the subject. Evaluable cytogenetic and BCR-ABL transcript analysis should be available prior to initiation of dosing. Bone marrow aspiration and/or BCR-ABL transcriptional analysis will be repeated if the results of the tests at screening are invalid or in-evaluable. For the aforesaid condition, subject will be dosed after confirmation of evaluable results prior to study drug administration and screening period will be extended for that subject, unless extension of screening period of subject's medical or disease condition after an evaluation of the impact of the extended period on assessment of efficacy and safety by the investigator and the medical monitor. For subjects with extension of screening period due to the aforesaid, treatment for underlying disease will be permitted with appropriate agents and stopped as per the requirement of exclusion criteria # 12 prior to study drug start.

Re-screening: Re-screening ([REDACTED]) is allowed and subjects will be reviewed on case-by-case basis in consultation with the medical monitors of the CRO and/or Sponsor. Reasons that may qualify for a re-screening include 1) expiry of screening period due to personal issue or timing or prior withdrawal of consent by subject 2) stabilization or discontinuation of prohibited concomitant medication 3) medical condition that has now resolved. However rescreening is not allowed if the previous failure was because of eligibility criteria that are unlikely to change (example: H/o allergy to the excipients, significant drug abuse, involvement in planning of study or rescreening patient subject's safety at risk, confirmed incorrect disease diagnosis). In case of re-screening, the subject will be assigned a different screening number.

Subjects will enter the study center [REDACTED] on Day 1 to receive the first administration of IMP and will complete the required assessments and sample collections ([REDACTED]). While K0706 should be preferably taken [REDACTED] the subjects should maintain [REDACTED] IMP dosing in all the cycles. Subjects may be admitted a day prior to Cycle 1 Day 1 dosing and if required stay overnight at the study center on Cycle 1 Day 1, based on Investigator's discretion. Subjects will complete the assessments on Cycle 1 Day 2 and may remain in the study center overnight for observation, at the discretion of the Investigator. Subjects will return for follow-up assessments ([REDACTED]) in Cycle 1 on Days [REDACTED].

Cycle 2 will have similar [REDACTED] sample collections on Day 1, and subjects will be required to return to the study center on Days [REDACTED] for [REDACTED] samples and other follow-up assessments. From Cycle 3 onwards, subjects will only be required to return to the study center once every [REDACTED] months ([REDACTED]).

Note: The last observation/evaluations for each cycle may coincide with the Day 1 of next

cycle e.g., Cycle 6 Day [REDACTED] observation may coincide with Cycle 7 Day 1). [REDACTED] samples will be collected on the day of the study visit from Cycle 3 onwards.

From Cycle 3, onwards, subjects will only be required to return to the study center once [REDACTED]

[REDACTED] Note: The last observation/evaluations for each cycle may coincide with the Day 1 of the next cycle e.g., Cycle 6 day [REDACTED] observation may coincide with Cycle 7 day 1). [REDACTED] samples will be collected on the day of study visit from Cycle 3 onwards. Subjects will return for a follow up- visit approximately 30 days after the last K0706 administration.

Subjects will remain on study treatment for approximately 60 months (i.e.: 5 years from 1st K0706 dosing), or until intolerance, subject withdraws from the study, or progression of disease. Subjects who discontinue the study will be followed up for survival (survival assessment includes information about subject survival and anticancer therapies) every 3 months (\pm 2 weeks) after the IMP discontinuation till 60 months from their first dose of K0706 or until death, withdrawal of consent, or the end of the study, whichever comes first.

Treatment beyond 60 months will be considered, provided the Investigator considers that the subject is benefiting from K0706 therapy. Subjects who continue to receive K0706 beyond 60 months will be followed up for safety, survival and response assessment. Information about subject's survival and disease response will be collected at the follow up visits every 3 months (\pm 2 weeks) in these subjects.

Subjects who experience a toxicity and recover, may be treated (at the Investigator and subject discretion) at the same dose or next lower dose level until disease progression or other events requiring dose reduction exist. [REDACTED]

[REDACTED] For additional details on dose delays and reduction refer to Section 7.4.2.1.

7.3.1.1 Dose Escalation Criteria

Dose escalation to a higher dose will not occur in the study. For details on dose delays and reductions, refer to Section 7.4.2.1 for details.

7.3.1.2 Study stopping rules

The study will be stopped prematurely

- If it is determined at any time during the study that the risk benefit is unacceptable for any reason, including recommendation by DSMB.
- For any other reason at Sponsor's discretion including discontinuation of development efforts

7.3.1.3 Discussion of study design

The study will be conducted in an open-label manner and all subjects will receive K0706. The rationale for the study and starting doses to be administered are presented in Section 7.1.

Appropriate safeguards for subject well-being and criteria for discontinuation of the K0706 in an individual subject and stopping rules are presented in Section 7.4.2.1 and 7.3.1.2 respectively.

A Data Safety Monitoring Board will be formed for periodic review of the safety data of the study. A formal charter will be generated that will describe the responsibilities of this group.

PK sampling and measurement of the drug concentrations will enable the assessment and comparison of the population PK profile of K0706. The duration of PK sampling has been chosen to sufficiently characterize the population PK of K0706.

7.3.1.4 Trial End points

7.3.1.4.1 Primary Endpoints

- Cohort A: For CML subjects in CP at study entry: major cytogenetic response (MCyR), defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR).
(CP subjects in CCyR are not eligible for this study)
- Cohort B: For CML subjects in AP at study entry: major hematologic response (MaHR), defined as complete hematologic response (CHR) or no evidence of leukemia (NEL). (AP subjects in MaHR are not eligible for this study)
- Cohort C: For CML subjects in BP at study entry: MaHR, consisting of CHR or NEL. (BP subjects in MaHR are not eligible for this study)

7.3.1.4.2 Secondary Endpoints

- In subjects with CML-CP, the objectives will be to evaluate the:
 - Hematological responses: Proportion of subjects who achieve or maintain complete hematological response
 - Cytogenetic response: Proportion of subjects who achieve CCyR
 - Molecular responses: Proportion of subjects who achieve major molecular response (MMR)
- In subjects with CML-AP, or CML-BP, the objectives will be to evaluate the:
 - Cytogenetic responses: Proportion of subjects who achieve CCyR, PCyR,
 - Molecular responses: Proportion of subjects who achieve MMR

- In all subjects: Safety and tolerability in terms of incidence and severity of treatment emergent AEs
- In all subjects: Time to response, duration of response, PFS and OS



7.3.2 Subject Population

Subjects with Ph+ CML-CP, Ph+ CML-AP, Ph+ CML-BP will be entered into the study provided that they satisfy the inclusion/exclusion criteria presented in Section 7.3.2.1. Up to approximately [REDACTED] subjects will be enrolled across the three cohorts of subjects contributed by a site should not exceed approximately 20% of total study population.

7.3.2.1 Subject Inclusion & Exclusion criteria

7.3.2.1.1 Subject Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria:

1. Willing and able to give written/signed, and dated, informed consent (inclusion of subjects needing legally acceptable representative/impartial witness will be in compliance to the enrolling country's regulatory requirement) and is available for the entire study
2. Willing and able to comply with the scheduled visits, treatment plan, laboratory testing, study procedures, and restrictions, and be accessible for follow-up
3. Subjects with Ph+ CML CP, AP or BP, who are resistant and/or intolerant to ≥ 3 prior TKIs one of which includes ponatinib. (Subjects with Ph+ ALL are not included)

Resistance is defined as documented evidence of any of the following applicable criteria on the prior TKIs*

| | CML-CP (Subject must meet at least 1 criteria) | CML-AP (Subject must meet at least 1 criteria) | CML-BP (Subject must meet at least 1 criteria) |
|---------------|---|---|---|
| Hematological | Three months after initiation of therapy: Failure to achieve CHR Or Loss of previously attained MaHR any time after initiation of TKI therapy (confirmed in at least 2 consecutive analyses at least 4 weeks apart) | Three months after initiation of therapy: Failure to achieve MaHR Or Loss of previously attained MaHR at any time after the initiation of TKI therapy (confirmed in at least 2 consecutive analyses at least 4 weeks apart) | One month after initiation of therapy: Failure to achieve MaHR Or Loss of previously attained MaHR at any time after the initiation of TKI therapy (confirmed in at least 2 consecutive analyses at least 1 week apart) |

| | | | |
|-------------|--|---|---|
| Cytogenetic | <p>Three months after the initiation of therapy: No cytogenetic response ($>95\%$ Ph⁺ cells)</p> <p>Or</p> <p>Six months after the initiation of therapy: Less than a minor cytogenetic response ($>65\%$ Ph⁺)</p> <p>Or</p> <p>Twelve months after the initiation of therapy: Less than a PCyR ($>35\%$ Ph⁺)</p> <p>Or</p> <p>Loss of cytogenetic response at any time after initiation of therapy (i.e.: shift of the cytogenetic response to at least 1 grade worse from the subject's most recently performed bone marrow cytogenetics: [e.g. from complete (0%) to partial (1% to 35%) to minor (36% to 65%) to minimal (66% to 95%)])</p> | Not applicable | Not applicable |
| Molecular | <p>Three months after the initiation of therapy: BCR-ABL 1(IS) $> 10\%$</p> <p>Or</p> <p>Twelve months after the initiation of therapy: BCR-ABL 1(IS) $> 1\%$</p> <p>Or</p> <p>Loss of Major Molecular Response (with 1- log increase in BCR-ABL transcripts) at any time during therapy</p> | Not applicable | Not applicable |
| Other | At any time after the initiation of therapy, development of new BCR-ABL mutations with loss of previously obtained response on the TKI (i.e.: Either hematological, cytogenetic or molecular response) | At any time after the initiation of therapy, the development of new BCR-ABL mutations with loss of previously obtained response on the TKI (i.e.: | At any time after the initiation of therapy, the development of new BCR-ABL mutations with loss of previously obtained response on the TKI (i.e.: |

| | | | |
|--|--|---|---|
| | <p>Or At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells with loss of previously obtained response on the TKI (i.e.: Either hematological, cytogenetic or molecular response) Or Any time after initiation of therapy: Progression from CML-CP to CML-AP</p> | <p>Either hematological, cytogenetic or molecular response) Or At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cell with loss of previously obtained response on the TKI (i.e.: Either hematological, cytogenetic or molecular response) Or Any time after initiation of therapy: Progression from CML-AP to CML-BP</p> | <p>Either hematological, cytogenetic or molecular response) Or At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cell with loss of previously obtained response on the TKI (i.e.: Either hematological, cytogenetic or molecular response)</p> |
|--|--|---|---|

*Intolerance is defined as documented evidence of any of the following applicable criteria on prior TKIs **

- Non-hematologic intolerance: Subjects with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments to the lowest doses recommended by manufacturer (80 mg QD for dasatinib; 400 mg QD for nilotinib; 300 mg QD for bosutinib; 15 mg QD for ponatinib), unless dose reduction is not considered in the best interest of the patient if response in the absence of a CCyR for CP subjects or MaHR for AP and BP subjects.
- Hematologic intolerance: Subjects with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer (80 mg QD for dasatinib; 400 mg QD for nilotinib; 300 mg QD for bosutinib; 15 mg QD for ponatinib) unless dose reduction is not considered in the best interest of the patient in the absence of a CCyR for CP subjects or MaHR for AP and BP subjects.

** Documented evidence will require laboratory reports substantiating resistance and/or intolerance on each TKI used by the subject prior to study entry*

4. Male or female aged ≥ 18 years
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
6. [REDACTED]

[REDACTED]

7. Subjects of childbearing potential must practice a medically acceptable effective method of birth control as judged by the Investigator:
 - a. Medically acceptable methods of birth control include the use of any of the effective birth control methods listed below-
 - i. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
 - ii. Progestogen-only hormonal contraception associated with inhibition of ovulation
 - iii. Placement of an IUD/ intra-uterine hormone releasing system. Consideration should be given to the type of device or system being

- used, as there are higher failure rates quoted for certain types, e.g., steel or copper wire
- iv. Intrauterine hormone-releasing system (IUS)
 - v. Same sex partner, a vasectomized partner/bilateral tubal occlusion
- b. The contraceptive method should be used continually within the past 3 months and the subject has to agree to continued use during the study and for 3 months after the last IMP administration.
 - c. To adopt another birth control method, or a double-barrier method which consists of a combination of any 2 of the following: diaphragm, cervical cap, condom, or a spermicide. The barrier method must be used in combination with another highly effective, non-barrier method (such as mentioned in Inclusion criteria # 7a) for at least 2 months prior to study entry and must continue to use contraception for the duration of the study and for 3 months after the last IMP administration.
 - d. Subject is postmenopausal for at least 1 year as per menstrual history or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy has been performed on the subject). For women < 45 years with menopausal symptoms, the menopause status to be reconfirmed by suitable laboratory tests including FSH level.
8. Male subjects enrolled in the study should not father a child and are advised to prevent passage of semen to their sexual partner during intercourse using an acceptable method as detailed in the Inclusion criteria # 7 and judged by the Investigator for the duration of the study and for 3 months after the last IMP administration
9. Female subjects of childbearing potential must have a negative pregnancy test (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin).
10. Female subjects must be non-lactating and non-breast-feeding.

7.3.2.1.2 Subject Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

- 1. Presence of T315I mutation
- 2. Any major surgery, as determined by the Investigator, within 4 weeks of IMP administration (Exceptions: Minor procedures such as bone marrow biopsy/aspiration, catheter placements and others procedures which in Investigator's opinion do not compromise subject safety)
- 3. Inability to swallow oral medication
- 4. Inability to undergo venipuncture and/or tolerate venous access

5. Evidence of clinically significant organ dysfunction or any clinically relevant deviation from normal in physical examination, ECG findings, vital signs, or clinical laboratory test findings which in the opinion of the investigator may jeopardize the safety of the patient during the study or may interfere with the evaluation of the study drug.
6. Positive tests: Urine pregnancy tests (if applicable), or HIV
7. History of any relevant allergy/hypersensitivity (including known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the IMP or its excipients)
8. Known history of active hepatitis B or hepatitis C
9. Received any other investigational agent within 30 days or a washout of at least 5 half-lives, whichever is longer of IMP administration
10. Use of concomitant medication that might influence the results of the study prior to IMP administration/or anticipated need any time during the study
11. Known or suspected history of alcohol abuse or excessive intake of alcohol in the 12 months prior to study entry
12. Known or suspected history of significant drug abuse as judged by the Investigator
13. Involvement in the planning and/or conduct of the study (applies to Sponsor, Contract Research Organizations, and study center staff, etc.)
14. [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
15. Active central nervous system (CNS) disease as evidenced by cytology or pathology. In the absence of active CNS disease, lumbar puncture is not required. History of CNS disease is not exclusionary if CNS disease has been cleared and documented by negative lumbar puncture and other necessary procedures at screening.

16. Malabsorption syndrome or other illness that could affect oral absorption of the IMP.

17. History of acute pancreatitis within 1 year of study or history of chronic pancreatitis

[REDACTED]

[REDACTED]

■ [REDACTED]
[REDACTED]
[REDACTED]

■ [REDACTED]
[REDACTED]
[REDACTED]

■ [REDACTED]
[REDACTED]

■ [REDACTED]
[REDACTED]

19. Uncontrolled intercurrent illness including, but not limited to the following: ongoing or active infection, uncontrolled seizure disorder, psychiatric or social circumstances that would limit compliance with study requirements or illness that, in the opinion of the Investigator, would compromise subject safety or interfere with the evaluation of the safety of the study drug.

20. Subjects who are eligible for potentially curative therapy that is available, including hematopoietic stem cell transplant

21. Autologous or allogeneic stem cell transplant \leq 3 months prior to Screening; any evidence of ongoing graft versus host disease (GVHD) or GVHD requiring immunosuppressive therapy \leq 28 days prior to the first IMP administration visit

22. Another primary malignancy within the past 3 years or earlier (except for adequately treated non-melanoma skin cancer or cervical cancer in situ).

23. Any contraindications for repeated bone marrow sample collection.

24. Prior exposure to K0706 therapy as a participant in Part B of the protocol.

7.3.2.2 Classification of CML subjects

Subjects will be classified as per the NCCN guidelines for Chronic Myeloid Leukaemia¹³ as follows

Table 7-2 Classification of Subjects with CML

| CML Phase | Criteria |
|-------------------|--|
| Chronic Phase | $< 15\%$ blasts in peripheral blood or bone marrow and $< 20\%$ basophils in peripheral blood and $< 30\%$ (blasts + promyelocytes) in peripheral blood or bone marrow and $> 100 \times 10^9$ platelets/L in peripheral blood and No extra-medullary disease |
| Accelerated Phase | $\geq 15 - < 30\%$ blasts in peripheral blood or bone marrow or $\geq 20\%$ basophils in peripheral blood or bone marrow or $\geq 30\%$ (blasts + promyelocytes) in peripheral blood or bone marrow (but $< 30\%$ blasts) or $\leq 100 \times 10^9$ platelets/L in peripheral blood unrelated to therapy or Additional clonal cytogenetic abnormalities in Ph+ cells |
| Blast Crisis | $\geq 30\%$ blasts in peripheral blood, bone marrow or both or Extra-medullary disease |

Note: For subjects wherein rapid disease progression is observed (beyond the aforementioned criteria) and subject safety is a concern, the subject can be discontinued at Investigator's discretion in consultation with Sponsor or Sponsor nominated CRO's medical monitor.

7.3.2.3 Criteria for Disease Progression

Table 7-3 Criteria for disease progression of subjects enrolled into the study

| Disease status at enrolment | Disease progression criteria | Reference |
|-----------------------------|--|------------|
| CML-CP | Progression to CML-AP or CML-BP at any time during the study Or WBC count that rises to $> 20.0 \times 10^9 / L$ ($> 20,000 / mm^3$) on two occasions at least 2 weeks apart (after first 4 weeks of K0706 therapy) in a subject Or | [REDACTED] |

| | | |
|---------------|--|------------|
| | Platelet count that rises to $> 600 \times 10^9/L$ ($> 600,000/mm^3$) on two occasions at least 2 weeks apart (after first 4 weeks of K0706 therapy) in a subject Or Loss of CHR (in the absence of a CyR) confirmed by complete blood counts done 4 weeks apart Or Loss of MCyR Or Death | |
| CML-AP | Development of confirmed BP Or Loss of previous major haematological response over a 2 week period Or No decrease from baseline levels in percentage blasts in peripheral blood or bone marrow on all assessments over a 4 week period (monitored at least every week) Or Death | [REDACTED] |
| CML-BP | Increasing blasts in peripheral blood or bone marrow over a 4 week period (monitored at least every week) Or Death | [REDACTED] |

Note: For subjects wherein rapid disease progression is observed (beyond the aforementioned criteria) and subject safety is a concern, the subject can be discontinued at Investigator's discretion

7.3.2.4 Restrictions

The following restrictions will apply to all subjects during the study.

- Women and men must continue birth control for the duration of the study and at least 3 months after the last administration of IMP. See Section 7.3.2.4.2 for acceptable forms of contraception

- Subjects should refrain from the use of concomitant medications that might reasonably influence the results of the study prior to K0706 administration and at any time during participation in the study. For restrictions regarding the allowed and disallowed medications, see Section 7.4.6.2.
- While K0706 should be preferably taken [REDACTED], the subjects should maintain approximately [REDACTED] IMP dosing throughout the study.

7.3.2.4.1 Avoidance of Pregnancy

Prior to study enrollment, women of childbearing potential (WOCBP) must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy.

Pregnancy should be avoided by either true abstinence or the use of 2 effective means of contraception (see Section 7.3.2.4.2) for the duration of the study and a total period of 3 months after the subject has taken the last administration of IMP.

Women of Childbearing Potential

Non-pregnant subjects and subjects of childbearing age must agree to use effective methods of contraception. All WOCBP must practice an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

All WOCBP MUST have a negative pregnancy test prior to first receiving IMP. If the pregnancy test is positive, the subject must not receive IMP.

In order to include WOCBP in any clinical study, certain precautions pertaining to pregnancy must be taken. These will include pregnancy testing at Screening, Day 1 of each cycle and the EoT visit.

Female subjects who become pregnant during the study will be withdrawn. If a subject becomes pregnant during the study, the pregnancy will be recorded as a significant medical event and reported per the SAE reporting procedures.

Women of Non-Childbearing Potential

Female subjects of non-childbearing potential are defined as women who had a bilateral oophorectomy/hysterectomy or are postmenopausal, having been amenorrheic for at least 12 months with an appropriate clinical profile, e.g., appropriate age, history of vasomotor symptoms.

Male Subjects

Men enrolled on this study should understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control.

As there is no information for K0706 being secreted in the ejaculate, male subjects (including men who have had vasectomies) including whose partners are currently pregnant should use barrier method for the duration of the study and a total period of 3 months after the subject has taken the last administration of IMP. This is to ensure that the fetus is not exposed to the IMP in the ejaculate.

There is no information about effects that K0706 could have on the development of the fetus in humans; however, K0706 is a teratogen and induces fetal toxicity in toxicology studies. Therefore, it is important that the partners of male subjects do not become pregnant during the study and for a total period of 3 months after the male subject has received the last administration of IMP.

7.3.2.4.2 Acceptable Forms of Contraception

Highly effective methods of birth control are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. These include female sterilization (i.e., documented bilateral tubal ligation), hormonal methods of contraception (oral, implanted, injected, or transdermal) or an IUD in combination with a barrier method (condom, diaphragm). Individually, hormonal, barrier or IUD methods alone are not acceptable.

Acceptable forms of effective contraception are:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation
- Placement of an IUD/ intra-uterine hormone releasing system. Consideration should be given to the type of device or system being used, as there are higher failure rates quoted for certain types, e.g., steel or copper wire
- intrauterine hormone-releasing system (IUS)

The following should be noted:

- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection
- Spermicides alone are inefficient at preventing pregnancy

7.3.2.4.3 Follow-up in the Event of a Pregnancy

If a female subject, or the female partner of a male subject, who has received K0706 becomes pregnant the pregnancy will be recorded on the Pregnancy Reporting Form. The pregnancy will be communicated to all stakeholders as per the local regulations. The subject will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise.

Spontaneous miscarriage, maternal/neonatal complications, and congenital abnormalities will be reported as SAEs. The follow-up period will be deemed to have ended when the health status of the child has been determined at birth.

7.3.2.5 Subject Withdrawals

The Investigator will make every reasonable attempt to have the subjects complete the study. However, a subject may withdraw from the study at any time without giving any reason. The Investigator will inform the Sponsor of the withdrawal of any subject.

A subject may be withdrawn in any of the following circumstances:

- Symptomatic or asymptomatic non-haematological Grade 4 toxicity
- Other adverse events such as Grade 3 hematologic/non hematological toxicities [or asymptomatic haematological Grade 4 toxicity hematological toxicities , clearly and incontrovertibly associated with use of K0706 confirmed with bone marrow assessment to delineate disease involvement of the bone marrow] not optimally managed with dose delays and reductions , which in the opinion of the Investigator, can affect overall subject's safety or requires measures which would not allow the continued fulfillment of the protocol requirements and restrictions
- Occurrence of new mutations along with signs/symptoms or laboratory evidence of disease progression
- Non-compliance with study and follow-up procedures
- Entry in another therapeutic clinical trial or start of additional anti-cancer therapy
- Protocol violation
- Pregnancy
- Subject is lost to follow-up
- Subject withdrawal of consent
- Progression of disease
- Termination of the study at Sponsor's discretion including discontinuation of development efforts

The Investigator should as far as possible have the subjects who withdraw complete the assessments at the EoT visit (see Section 11.2). The EoT visit should be completed within 30 days or earlier after withdrawal of the subject. In cases of disease progression, necessitating initiation of an alternative anti-leukemic treatment, the EoT treatment can be completed at an earlier time point within the 30 days after withdrawal of the subject.

- 1) If EoT visit has occurred within 30 days (± 5 days) from last IMP administration and all EoT assessments have been completed, a separate 30 day safety follow-up after last dose should be completed: The decision of using either telephonic discussion/ site visit/medical record review for the 30 day safety follow up will be based upon investigator's assessment of the need basis subject's clinical history and clinical condition.
- 2) If EoT visit has occurred within 30 days (± 5 days) from the last IM administration and all EoT assessments have not been completed, a separate 30 day safety follow-up from the last dose should be completed: In these cases, assessments which have been missed on EoT visit, may be done at the 30 day safety follow-up visit. If based upon investigator's assessment of the subject's clinical history and clinical condition the recommendation is for using either telephonic discussion/medical record review instead of site visit for the 30 day safety, consultation with Sponsor's medical monitor should be sought for the missing EoT parameters.
- 3) If at EoT/30 day safety follow up visit there are any unresolved AEs/SAEs, they will be followed until resolution or until the event is stabilized or until it can be explained by another known cause (i.e. concurrent condition or medication) as per medical judgement of the investigator. The follow up methodology will be based on investigator's discretion and subject's clinical history and clinical condition. Any SAE reported by the patient after the completion of AE collection period and considered related to the study drug should also be reported by the investigator. Disease progression is not considered an AE in this study unless it leads to death or hospitalization in which case it needs to be reported as SAE.

Subjects will continue to be followed for survival.

Subjects who withdraw before first post baseline efficacy assessment in the study will be replaced unless the withdrawal is due to AE related to K0706 or disease progression. All efforts will be taken to keep the subjects withdrawn at $\leq 10\%$ of the proposed sample size per disease cohort.

7.4 STUDY TREATMENT

7.4.1 Investigational Medicinal Product(s)

All the subjects will receive a continuous once daily oral administration of K0706 in a [REDACTED] cycle.

7.4.1.1 K0706

[REDACTED]

Table 7-4 Details of K0706

| | |
|----------------|---|
| K0706 capsules | <p>Description:</p> <p>[REDACTED] capsules with blue cap and off-white body, axially imprinted with two bar lines on cap and body</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> |
|----------------|---|

See Section 7.4.2 for details on the doses to be administered in the study. Please see the IB for further information on K0706.

7.4.1.2 Placebo

No placebo will be administered.

7.4.1.3 Supply, Packaging and Labelling

The IMP will be supplied to the study centers by a Contract Research Organization appointed by the Sponsor.

A sufficient quantity of [REDACTED] capsules prepared for the human studies containing K0706 will be supplied to the study centers. The capsule for K0706 will be manufactured by SPARC/SPARC approved vendor and stored in compliance with GMP conditions and labelled in accordance with local regulations.

Individual subject treatments will be dispensed by the study center pharmacist in appropriate containers with child-resistant twist-off caps. All clinical study material will be packaged and labelled to comply with applicable regulations. The IMP will be clearly labelled according to local requirements regarding use for clinical study investigation only and will be labelled with the IMP name, protocol number, Kit number, Lot number, expiry date, date dispensed, Subject number, study center number, storage conditions, and Sponsor details. Details may be added or deleted depending upon the local regulatory requirements in the participating countries. Separate documentation regarding the expiry or retest date will be made available.

Dispensing of the IMP to the subject and reconciliation of the returned IMP will be documented by the site staff. A technical agreement between the study center and the CRO will be in place to cover all pharmacy related activities, detailing roles and responsibilities prior to receipt of the IMPs at the study center.

7.4.1.4 Storage and Handling Procedures

The IMPs will be stored as below:

Store at room temperature [REDACTED] in a tightly closed container protected from light and moisture. Excursions are permitted to [REDACTED]. The storage area of the study centre, will be a secure, temperature controlled, and locked environment with restricted access.

7.4.1.5 Accountability

In accordance with GCP, the study center will account for all supplies of K0706. Details of receipt, storage, assembly, and return will be recorded.

All unused supplies of K0706 will either be destroyed by a designated vendor or will be returned to the study Sponsor at the end of the study in accordance with instructions by the Sponsor.

7.4.2 Dosage and Administration

K0706 capsules will be self-administered. The subject should be instructed about the following.

- While K0706 should be preferably taken [REDACTED], the subjects should maintain approximately [REDACTED] K0706 dosing throughout the study.
- Water will be permitted [REDACTED] K0706 administration and again from [REDACTED] K0706 administration.
- Subjects should be instructed to take their K0706 dose at approximately the same time each morning.
- On days where blood for [REDACTED] samples need to be collected before taking study drug, the patient should take the K0706 dose at the clinic.
- If the patient forgets to take his/ her daily K0706 dose, then he/ she should take it within 6 hours after the missed dosing time. If more than 6 hours have passed, then that dose should be omitted and the patient should continue treatment with the next scheduled dose.
- If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose.

In the study, the subject will be required to return to the study center to receive their administration of K0706 for the first 3 days of Cycle 1. After administration of K0706 on

Cycle 1 Day 3, the subject will be dispensed with a sufficient amount of K0706 to last for the remainder of Cycle 1. From Cycle 2 onwards, a sufficient amount of K0706 to last until at least the subject's first scheduled visit of the next cycle will be dispensed to the subject on the first day of the cycle.

The subject will be required to bring the dispensed K0706 to the study center at each visit and the Investigator is to confirm the number of capsules taken and remaining before returning K0706 to the subject.

The subject will also be supplied with a diary card on which is to be recorded the date and time K0706 is taken, meals timings before and after IP consumption as well as any other medications that the subject may have taken during the course of the day (along with the reason for taking the medication). The diary will be dispensed on visits on which there is site visit and the subject will be required to bring the diary to each visit to the study center where the Investigator will review the diary and record the details into the eCRF.

The date and time when K0706 is administered will be documented in the subject's diary card and eCRF. Additionally, the following should be recorded

1. Was the IMP taken [REDACTED] (yes/no and if no the timing of the last meal)
2. First meal/food consumption after the IMP administration

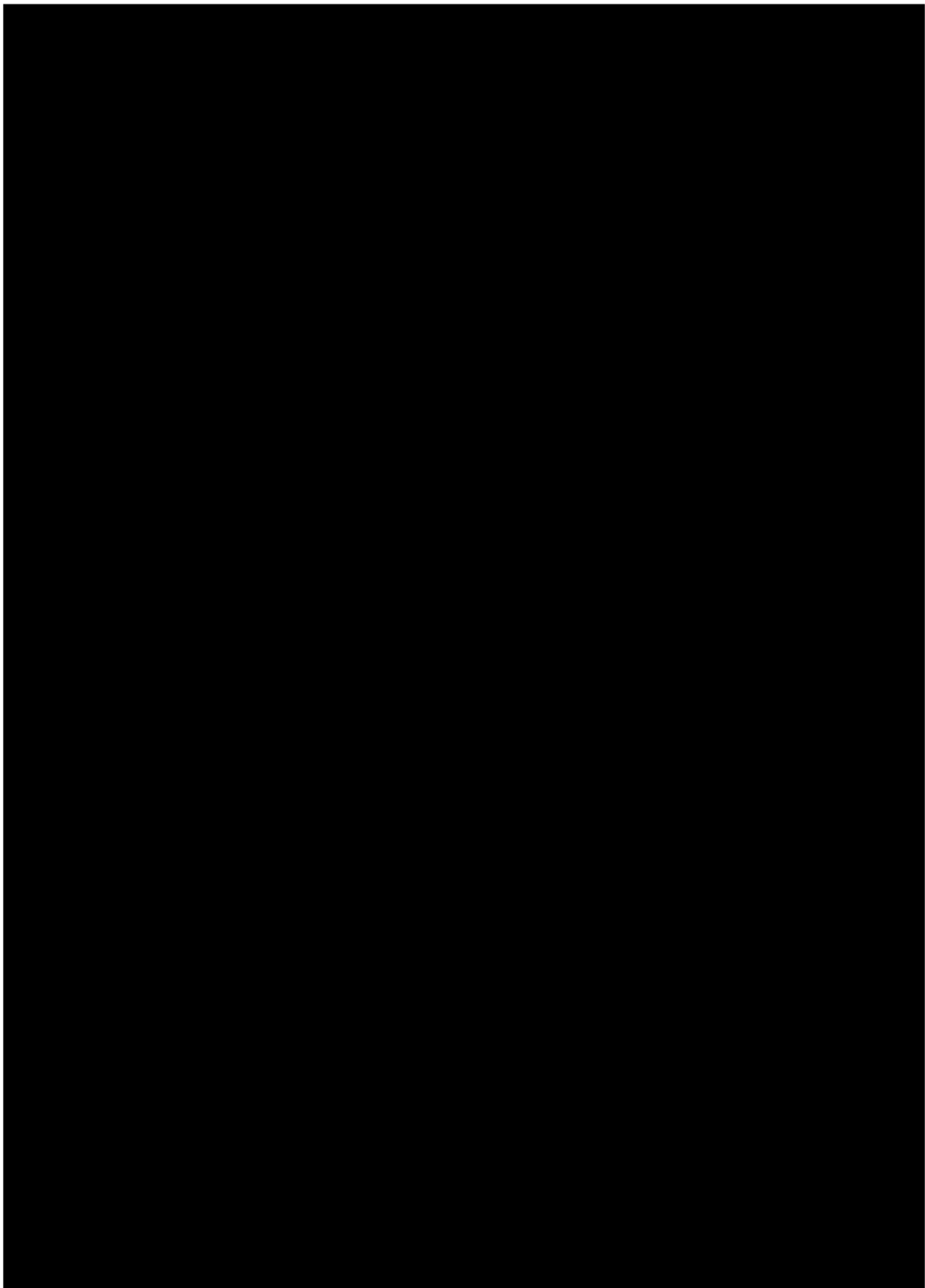
7.4.2.1 Dose Delays and Reduction

This section provides guidance for study drug related toxicities graded according to NCI CTCAE Version 5.0. Dose delays or reductions or both may be implemented for subjects who experience adverse drug reactions with K0706 as per the Table 7-5. [REDACTED] reductions will be permitted (i.e., [REDACTED]). Further dose reduction or delay or both may be implemented basis joint discussion between investigator and sponsor's medical monitor basis evaluation of subject's clinical condition. [REDACTED]

Moreover, after resolution of the event the investigator may resume the subject on the same dose (i.e., dose administered in the previous cycle) if clinically acceptable.

[REDACTED]

[REDACTED]



[REDACTED]

[REDACTED]
 [REDACTED]
 [REDACTED]

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

7.4.2.2 Management of Missed Doses

Subjects who miss their scheduled dose of study drug should be instructed to not make up for the missed doses. If the patient forgets to take his/ her daily dose, then he/ she should take it within 6 hours after the missed dosing time. If more than 6 hours have passed, then that dose should be omitted and the patient should continue treatment with the next scheduled dose. The missed doses should be recorded in an appropriate source document and the CRF (Example: Patient diary, study drug administration record).

7.4.3 Treatment Strategy

The staff at the study centers are all responsible for the ongoing safety and well-being of the subjects while they are resident in the study centers.

It is expected that study centers participating in this study will have a working system/method (such as, but not limited to, a paging system, emergency phone lines, etc.) to alert the staff to any area in the unit where a subject may need medical attention. In the case of an emergency, cardiac resuscitation trolleys will be available in the main ward areas of the study center. These trolleys contain drugs, equipment for airway insertion,

circulation lines, defibrillation etc., together with oxygen cylinders and portable suction machines. Physicians will be present for dosing and close observation over the first 8-12 hours after IMP administration.

If necessary the clinical staff can contact further on-call physicians or public emergencies services, including an ambulance, in the event of a serious medical event. The site should be equipped for anticipated emergencies in this patient population.

7.4.4 Monitoring and study drug administration

Subjects will be provided a Patient diary or its equivalent. Subjects will be provided training on use of the subject diary by the site. Subjects who miss their doses will be instructed to not make up for the missing doses within 6 hours. Subjects will be instructed to enter all the missed doses in the subject diary. Whenever possible, subjects should take the study drug under observation during scheduled study visits to the clinic. A scanned copy of the subject diary should be maintained by the CRO and sent across to the sponsor at the end of every cycle for the first 3 cycles and thereafter at the end of every 3 cycles (i.e. end of Cycle 6, 9, 12 and beyond)

7.4.5 Warnings and Precautions

Although the effects of similar TKIs are known, all effects of K0706 cannot be reliably predicted. The preclinical data suggest an acceptable safety margin. See the IB for details on events that could be expected.

Use of anti-clotting agents

Serious bleeding events, including fatalities have occurred in patients treated with TKIs like imatinib mesylate, dasatinib and ponatinib. The incidence of serious bleeding events was higher in patients with CML-AP and CML-BP. Cerebral hemorrhage and gastrointestinal hemorrhage were the most commonly reported serious bleeding events. Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia. Caution is indicated in patients requiring medications that inhibit platelet function or anticoagulants.

Use of Cytochrome inhibitors

Tyrosine kinase inhibitors should be used with caution when concurrently used with moderate and strong CYP3A inhibitors (such as clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit juice) and moderate or strong CYP3A inducers (such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort). Sensitive substrates of CYP2C8 with a narrow therapeutic index should be avoided or used with caution in this trial (Refer to section 7.4.6.1).

7.4.6 Prior and Concomitant Medication

See section 7.4.6.1 for precautions with regards to the use of anti-clotting agents and CYP inhibitors.

Any medications (other than those excluded by the inclusion/exclusion criteria) that are considered mandatory for the subjects' safety/well-being and that are not anticipated by the Investigator to be likely to interfere with the IMP, may be given at the discretion of the Investigator. In the interest of subject safety and acceptable standards of medical care for subjects with cancer, the Investigator will be permitted to prescribe supportive treatment(s) or palliative bone-directed radiotherapy at his/her discretion.

Medications other than those specifically excluded in this study may be administered for management of symptoms associated with administration of K0706 as needed. These medications include analgesics, anti-nausea medications, antihistamine, antianxiety medications, and medication for pain management (narcotic agents are included).

7.4.6.1 Medications and therapies with restrictions

As stated in the exclusion criteria, subjects must not have had prior therapy with any investigational drug within 30 days before the start of K0706 administration or with BCR-ABL TKI as per exclusion criteria # 13 before the start of K0706 administration.

In addition, the following treatments must not be administered during the study: Immunotherapy, immunosuppressive drugs and Growth factors (other than mentioned in section 7.4.6.2)

Sensitive substrates of CYP2C8 with a narrow therapeutic index, along with strong inhibitors or inducers of major CYP enzymes, should be avoided or used with caution in this trial

Medications that are strong inhibitors and strong inducers of CYP3A4 include, but are not limited to those listed below:

| | | |
|------------|------------|------------|
| [REDACTED] | [REDACTED] | [REDACTED] |
| | | [REDACTED] |
| | | [REDACTED] |
| | | [REDACTED] |
| | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| | [REDACTED] | [REDACTED] |
| | | [REDACTED] |
| | | [REDACTED] |

Clinically significant CYP2C8 substrates include, but are not limited to those listed below:

| | |
|------------|------------|
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |

Sensitive substrates of P-gp and BCRP with a narrow therapeutic index, should be avoided or used with caution.

| | |
|------------|------------|
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |

The following nondrug therapies must not be undertaken or administered during the study (or within 4 weeks before the start of IMP administration):

- Major surgery (excluding diagnostic biopsy)
- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin)
- Subjects should not abuse alcohol or other drugs during the study

7.4.6.2 Permitted medications

- Short-term administration of systemic steroids (that is, for allergic reactions or management of immune- or infusion-related AEs) is allowed.
- Granulocyte-Colony stimulating factor, Erythropoietin and darbepoetin-alpha as exceptions may be prescribed at the discretion of the Investigator.
- Transfusion of blood and related products such as platelet or red blood cells may be prescribed at the discretion of the Investigator.
- Where appropriate, hydroxyurea or anagrelide are permitted during the first cycle of K0706 administration. Concomitant use must be discontinued by the end of the

third week of K0706 in subjects with AP, BP and by the end of the first cycle in all patients, and is thereafter prohibited.

7.4.7 Method of Assigning Subjects to Treatment Groups

At Screening, potential study subjects will be assigned a Screening number. Following confirmation of eligibility, before IMP administration, subjects enrolled will kept the same screening number

7.4.8 Randomization Procedures

All eligible subjects will be assigned to treatment with K0706. Enrollment into the assigned cohorts will be parallel.

7.4.9 Maintenance of Randomization Codes

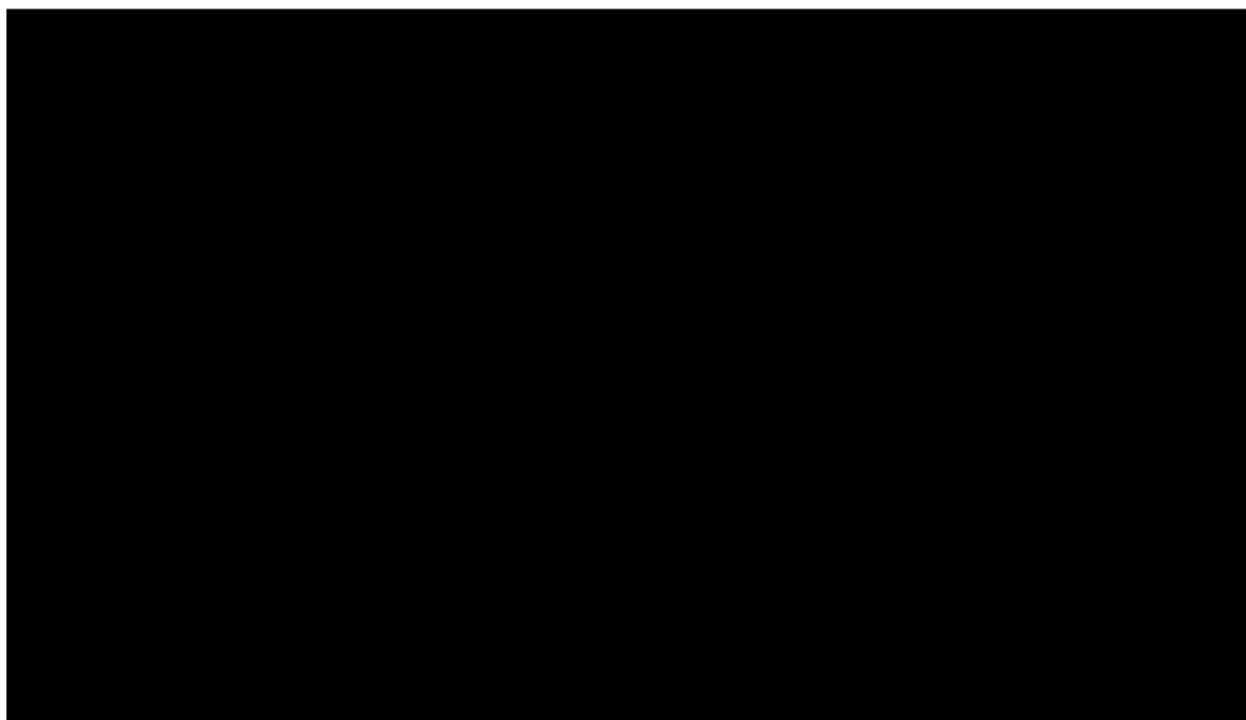
Not applicable.

7.4.10 Blinding

The study will be open-label.

7.5 STUDY PROCEDURES

The Schedule of Assessments to be performed in the study is presented in Section 11.2. The approximate volume of blood to be collected from each subject in a given cohort in the study provided in the table below.



[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

7.5.1 Pharmacokinetic Assessments

Plasma Samples

Blood samples ([REDACTED]) will be collected at specified time points to determine plasma concentrations of K0706. Blood sample collection times are included in the schedule of assessments (see Section 11.2).

Individual venipunctures for each time point may be performed or an indwelling catheter may be used. If the study center chooses to use an indwelling catheter, the first 1 mL (approximately) of blood will be discarded and the catheter flushed with saline following each sampling. Heparin may not be used to flush the catheter. The exact date/time of the blood sample collection will be recorded in the subject's eCRF.

The plasma obtained from the PK samples will be split into 2 cryogenic tubes, with 1 tube shipped to the bioanalytical laboratory. The remaining cryogenic tube will be retained as a back-up sample. Details of sample collection procedures, sample preparation (if applicable), sample collection tube, sample labelling, sample storage and sample shipment will be described in a separate Laboratory Manual.

Serial PK sampling will be performed [REDACTED]

Bioanalysis

Determination of the plasma concentrations of K0706 will be performed using a validated method. The details on the analytical methods used will be described in a separate bioanalytical report.

7.5.2 Efficacy Assessments

Detailed collection tubes, sample processing, label, storage, and shipment information will be described in the Laboratory Manual. The details of the analytical methods used will be described in a separate bioanalytical report. Biological samples collected during the conduct of the study will be retained for a period of up to 2 years after study closure, not exceeding the time strictly necessary for the fulfillment of the purposes of the study; samples could be stored for a longer duration as per applicable regulatory requirements.

Serum, blood, and bone marrow-based samples will be collected at specified time points to assess the efficacy endpoints of interest, see section 7.5.4, 7.5.5 for more details.

Sample collection times are included in the schedule of assessments (see Section 11.2).

7.5.2.1 Mutation Profiling

Mutation testing for BCR-ABL sequencing will be performed on peripheral blood and/or bone marrow samples.

The BCR-ABL mutation profiling may be done by Sanger (direct) sequencing as a primary assay. Quantitative reverse transcript-PCR may be used as an exploratory assay. Sample logistics and the location of testing will be detailed in the Laboratory Manual.

7.5.2.2 Cytogenetic Response

Bone marrow aspirate samples will be sent for review of cytogenetics by [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

For subjects who demonstrate complete cytogenetic response on two repeated assessments, bone marrow aspirate samples may be collected at 6 monthly intervals thereafter.

Standard cytogenetic methods will be used to determine the presence of the Ph+ and its presence (percentage) in the bone marrow. At least [REDACTED] cells in metaphase will be evaluated for karyotyping. [REDACTED]

Cytogenetic response is a response to treatment of CML that occurs in the bone marrow, rather than just in the blood. A cytogenetic response means any Ph+ chromosome reading obtained after K0706 administration interpreted as described below.

There are 3 levels of cytogenetic response:

1. Partial Cytogenetic Response (PCyR): This indicates that only 1 to 35% of the sample contains Ph+ metaphases
2. Complete Cytogenetic Response (CCyR): This indicates no Ph+ cells can be measured by either conventional or fluorescence in situ hybridization cytogenetic testing (though the PCR test may still be positive)
3. Major Cytogenetic Response (MCyR) is cytogenetic response inclusive of PCyR and CCyR

Sample logistics and the location of testing will be detailed in the Laboratory Manual.

7.5.2.3 Major Molecular Response

Molecular response monitoring (MMR) using PCR for BCR-ABL copy number will be performed on the collected blood samples and will be assessed using the international scale as per the schedule of assessments.

A molecular response is defined as a negative PCR or other negative molecular test. A PCR test is defined as a very sensitive test which can be used to detect the presence of very low levels of specific genetic material (DNA). It is used to detect, and sometimes to quantify, BCR-ABL in bone marrow cells of subjects with CML. The most sensitive PCR tests can detect as few as one in 100,000 copy number/mL.

An MMR indicates that the amount of BCR-ABL protein in the bone marrow is very low: BCR-ABL transcripts is 0.1% by quantitative PCR (IS) or ≥ 3 -log reduction on BCR-ABL mRNA from the standardized baseline if quantitative PCR (IS) is not available.

A complete molecular response indicates that no BCR-ABL protein can be detected in the marrow utilizing the PCR test: no detectable BCR-ABL mRNA by quantitative PCR (IS) using an assay with a sensitivity of at least 4.5 logs below the standardized baseline.

Sample logistics and the location of testing will be detailed in the Laboratory Manual.

7.5.2.4 Hematologic Response

A hematological response is a normalization of the blood counts, particularly WBC counts. This is the first noticeable indicator that treatment is beginning to work, though not necessarily in the bone marrow. The response can be a partial hematological response (reduction in WBC, but not down to normal range) or CHR.

The CHR will be evaluated by peripheral blood utilizing local laboratory results.

A CHR is usually anticipated within [REDACTED] of treatment, however, some subjects may take longer to achieve this level. The [REDACTED]
[REDACTED]

Refer to Appendix I and Operations Manual for the definitions of CHR and MaHR.

Sample logistics and the location of testing will be detailed in the Operational Manual.

7.5.3 Safety Assessments

7.5.3.1 Adverse Events

The safety and tolerability of subjects will be assessed by the incidence of treatment emergent AEs, study drug discontinuation information, laboratory test results, vital signs, ECGs and physical examination findings.

Definitions:

Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, be related to study procedures or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Untoward medical experience occurring during medication-free pre-treatment periods does not meet the above-mentioned definition of an AE. Nevertheless, they have to be documented in the same way as AE. Each subject will be queried generally for the occurrence of adverse experiences prior to study drug administration and throughout the subject's participation in the study. During and following a subject's participation in this study, the Investigator has to ensure that adequate medical care is provided to a subject for any AE, including clinically significant laboratory values.

The investigator will document all AEs in the subject's source document and eCRF. All entries should contain an event term, date of onset, date of resolution, severity, action taken, outcome, relationship to study drug, and a seriousness assessment.

Adverse Drug Reaction

An adverse drug reaction is an "untoward and unintended response to an IMP related to any dose administered".

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse drug reactions. The expression of "reasonable causal relationship" means to convey in general that there are facts or arguments which suggest a causal relationship.

Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that, at any dose

- Results in death
- Is life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization*
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important Medical Event or requires medical intervention to prevent one of the outcomes listed above.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (eg, sudden death, unexplained death), the death per se might then be reported as an SAE.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which, hypothetically, might have caused death if it were more severe.

*A planned hospitalization for pre-existing condition/s, or a procedure required by the Clinical Investigation Plan; minor procedures without a serious deterioration in subject's health (e.g.: catheter or feeding tube placements etc.) or hospitalization clearly unassociated with an AE (e.g., social hospitalization, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not to be considered as SAEs. Any Hospitalization due to social and logistic reason will not be considered as SAE. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Treatment-Emergent Adverse Event

TEAEs are defined as any AE occurring or worsening on or after the first dose of IMP.

Unexpected Adverse Event

Any AE that is not identified in nature, severity, frequency or outcome in IB will be considered as unexpected. The IB version effective at the time of onset of the event will be used for assessment of expectedness of SAE. [Note: The effective date of an IB version is referring to the last RA approval date of the IB version in EU countries.]

Additionally, the Principal Investigator will evaluate all AEs as follows:

Seriousness: whether or not the AE is fatal or life threatening, persistent or permanently disabling, requires or prolongs inpatient hospitalization, is a congenital anomaly or an important medical event.

Action taken with study drug: Action taken is categorized as “none”, “study drug discontinued/withdrawn”, “study drug discontinued temporarily and restarted”, “dose modified”, or “not applicable”.

Event Outcome: Event outcome, or time last follow-up is recorded is categorized as “Fatal”, “Resolved”, “Resolved with sequelae”, “Resolving”, “Not Resolved”, “Unknown”.

Any AE that is not identified in nature, severity, frequency or outcome in IB will be considered as unexpected. The IB version effective at the time of onset of the event will be used for assessment of expectedness of SAE. [Note: The effective date of an IB version is referring to the last RA approval date of the IB version in EU countries.]

Categorization of Adverse Events

The grading scales found in NCI CTCAE v5.0 will be utilized for all AEs with an assigned CTCAE grading. For those AEs without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (<http://evs.nci.nih.gov/ftp1/CTCAE/About.html>).

If a particular AE's intensity is not specifically graded by the guidance document, the Investigator is to use the general NCI CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are as follows:

Intensity, to be graded as:

| Degree | Description |
|------------------|--|
| Mild | Awareness of signs and symptoms; easily tolerated |
| Moderate | Discomfort sufficient to interfere, but not prevent daily activity |
| Severe | Unable to carry out usual activity |
| Life threatening | Life-threatening consequences; urgent intervention indicated. |
| Death | Death related to AE. |

Relationship to study drug, to be graded as:

| TERM | DEFINITION | CLARIFICATION |
|-----------|---|--|
| Unrelated | Those AEs which, after careful consideration, are clearly due to extraneous causes (medical history, demography details, disease, environment, <i>etc.</i>) | |
| Unlikely | A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. | <ol style="list-style-type: none"> 1. It does not follow a reasonable temporal sequence (Improbable temporal relationship) from administration of the drug. 2. It could also be explained by patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions |
| Possibly | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. | <ol style="list-style-type: none"> 1. It follows a reasonable temporal sequence from administration of the drug. 2. It could also be explained by patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals (including food-drug interactions). 3. There is no information or uncertainty with regard to what has happened after stopping the drug. |
| Probably | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition. | <ol style="list-style-type: none"> 1. It follows a reasonable temporal sequence from administration of the drug. 2. It could not be readily explained (unlikely) by the patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions. 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. 4. No rechallenge information is available or possible. |
| Certainly | A clinical event, including laboratory test abnormality, occurring in a plausible time | <ol style="list-style-type: none"> 1. It follows a plausible time sequence to drug intake, this means that there is a positive argument in sufficient detail to support the view that the drug is |

| TERM | DEFINITION | CLARIFICATION |
|------|---|--|
| | relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary. | <p>causally involved, pharmacologically or pathologically e.g. pharmacokinetics and type of reaction.</p> <p>2. It could not be explained by patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions (i.e. no alternative causes).</p> <p>3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible.</p> <p>4. It is an objective and specific medical disorder or a recognized pharmacological phenomenon for instance 'grey baby syndrome' and chloramphenicol or anaphylaxis immediately after the administration of a drug that had been given previously. <i>This means that any other event is automatically excluded and can never qualify for 'Certain' (even in the case of a positive rechallenge observation).</i></p> <p>5. It reappears on readministration of the drug (only if ethically correct i.e. in case of non-serious, and easily treatable AEs).</p> |

Assessment of Expectedness

The IB version effective at the time of onset of the event will be used for assessment of expectedness of SAE. [Note: The effective date of an IB version is referring to the last RA approval date of the IB version in EU countries.]

Additional guidance on the AE/SAE reporting

For AEs:

- AE reporting period for safety surveillance begins after subject is randomized into the study and receives at least 1 dose of IMP for treatment emergent adverse events (TEAEs) and continues until 30 days from end of treatment visit. Any AE which occurs 30 days after end of treatment visit or last dose of IMP will be reported if it is considered related to IMP/study procedure by the investigator.
- All physical examination (PE), medical history, and laboratory findings considered to be clinically significant and baseline events occurring post-consent, but prior to receiving the first dose of study medication will be classified and graded according to CTCAE nomenclature but will not be considered AEs and entered in subject's medical history.
- All study procedure related events occurring post consent and prior to first IMP administration will be recorded as Non Treatment Emergent Adverse Events (Non TEAEs).
- Disease progression as defined in Section 7.3.2.3 or as per clinical judgement of Investigator is not considered as an adverse event in the study, unless it leads to hospitalization or death in which case it should be reported as SAE. Subjects with disease progression should be discontinued from the study and their EoT visit be performed at the earliest.

For SAEs:

- SAE reporting period for safety surveillance begins after the subject consents for the study and continues until 30 days from end of treatment visit or last dose of IMP will be reported if it is considered related to IMP/study procedure by the investigator.
- All SAEs occurring prior to receiving the first dose of study drug will be recorded as Non TEAEs. Site as well as Sponsor/Sponsor's designee will comply with any additional reporting requirements of the EC/IRB and applicable local regulations.
- All deaths occurring in the study will be reported as SAEs to the Sponsor. Site as well as Sponsor/Sponsor's designee will comply with any additional reporting requirements of the EC/IRB and applicable local regulations.

Follow up of unresolved AEs: Any AE/SAE unresolved at end of study visit will be followed until resolution or until the event is stabilized as per medical judgement of the investigator.

Events Not to Be Considered as AEs/SAEs

Medical, baseline, pre-dosing conditions present at the initial study visit (i.e.: screening visits) that do not worsen in severity or frequency during the study, are defined as Baseline Medical Conditions and are not to be considered AEs.

For criteria pertaining to disease progression please refer to guidance in the aforementioned text on Additional guidance on AE/SAE reporting.

Suspected Unexpected Serious Adverse Reactions and Unexpected Adverse Reactions

Any suspected adverse reaction that is serious, unexpected, and considered to be related to drug exposure is defined as a SUSAR.

7.5.3.2 Reporting of Serious Adverse Events

All SAEs must be reported according to ICH GCP or local regulations, applying the regulation with the stricter requirements. The report will contain as much available information concerning the SAE to enable the Sponsor's safety physician/CRO to file a report, which satisfies regulatory reporting requirements. The SAE report will be notified by Investigator within 24-hours of his/ her awareness to the Sponsor's safety physician/CRO. These timelines apply to initial reports of SAEs and to all follow-up reports.

All AEs/SAEs will be recorded on the AE Report Form and SAE report form in the eCRF and source documents.

The following minimum information must be included in the SAE form:

- Name, address and telephone number of the reporting Investigator
- IP details
- Subject identification number, initials, sex and date of birth
- Description of the SAE, measures taken and outcome

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor's safety physician/CRO may have on the SAE. This is necessary to ensure prompt assessment of the event by the Sponsor's safety physician to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

The contact details of Sponsor's safety physician are as follows:

Safety Physician

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Follow-up

Any unresolved AE/SAE will be followed up till resolution/stabilization or as per medical judgement of the investigator. The Investigator should take all appropriate measures to ensure the safety of the subjects, including referral to a specialist if indicated.

7.5.3.3 Pregnancy

A pregnancy test will be performed at screening and at visits specified in the protocol. Females of childbearing potential must not be pregnant or lactating (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin). Females of childbearing potential must agree to the use of a reliable method of contraception as described in Inclusion Criteria of this protocol and throughout the study. Subjects with a positive test at screening or during the study period will be excluded from study. Similarly, male subjects enrolled to the study will be instructed not father a child and avoid passage of semen to their partner by using an acceptable contraceptive method as discussed by the investigator during the enrolment to the study. However, if a female subject becomes pregnant during the study, the pregnancy will be recorded as a significant medical event and reported per SAE reporting procedure and the subject will be withdrawn from the study immediately. Similarly, if a female partner of a male subject becomes pregnant during the study, the medical event will be recorded appropriately. The 'pregnancy reporting form' will be completed and submitted to Sponsor. The pregnancy shall be followed every three months till its outcome and up to one month post-delivery to assess the functional status of the child. If any SAE occurs during pregnancy then it will be reported using SAE forms as per timelines defined in section above. Any congenital abnormalities or birth defects in the newborn will be followed three months post-delivery.

7.5.4 Clinical Laboratory Safety Tests

Sample collection times are included in the schedule of assessments (see Section 11.2).

Clinical Laboratory tests including hematology, coagulation, clinical chemistry, and urinalysis will be performed. The details of the tests to be performed will be provided separately in the Operation's Manual. Other laboratory tests to be performed are shown

below. Testing for Human immunodeficiency virus I and II will be done in serological examinations.

Additional and repeat testing may be performed at the discretion of the Investigator.

Unless otherwise specified in the Operation's Manual, the safety laboratory tests will be performed by the study center's local laboratory. Details of all methodology and reference ranges are provided in the Laboratory manual and Trial Master File.

The clinical laboratory test results will be reviewed for potential clinical significance by the Investigator. If the Investigator determines a laboratory value to be outside the normal laboratory range of the local testing laboratory and clinically significant, it should be considered an AE (and should be documented as such); however, if the laboratory value abnormality is consistent with a current diagnosis, it may be documented accordingly.

Urine pregnancy tests will be performed at the time points stipulated in the schedule of assessments (see Section 11.2).

7.5.5 Clinical Safety Assessments

Assessment times are included in the schedule of assessments (see Section 11.2).

7.5.5.1 Vital Signs

Vital signs (including blood pressure [systolic and diastolic], pulse rate, respiratory rate, and temperature) will be measured in a supine position after the subject has rested comfortably for at least 5 minutes using an automated instrument.

Additional vital signs measurements may be performed for the safety of the subjects. The vital signs measurement results will be reported in the subject's eCRF.

If clinically significant findings, as determined by the Investigator, occur in any of the vital signs measurements, that measurement will be repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

7.5.5.2 12-Lead Electrocardiogram

A computerized 12-lead ECG (single replicate) will be performed with the subject in a supine position after the subject has rested comfortably for at least 10 minutes. The 12-lead triplicate ECGs (10 sec recordings) spaced approximately 1 minute apart will be performed at Screening, Cycle 1 Day 1 and Day of Subject Discharge from the study Centre. Similar ECG is to be performed predose and at 2 and 4 hours from K0706 administration, time points which are most likely to correlate with maximum plasma K0706 concentration. For subsequent cycles ECG will be performed postdose on study visit days. At investigator's discretion and/or availability of new information from the study more frequent ECG monitoring may be performed if clinically indicated. The ECGs

will be performed and be duplicated on days of PK sampling, 1 to 2 minutes apart. Single ECGs will be performed on days of non-PK sampling.

The Investigator, or a designee, will report whether the ECG is normal or abnormal and if the result is considered clinically significant or not. All clinically significant ECG abnormalities occurring during the study should be documented as AEs.

Standard ECG parameters, including heart rate, QRS, PR interval, RR interval, QT interval, and the QTc using Fridericia's formula will be measured. The ECGs will be read by the Investigator, or a designee, to assess any abnormalities.

7.5.5.3 Medical, Surgical, and Medication History

A complete medical history will include evaluation (past or present) of the following: general, head and neck, eyes, ears, nose throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, gynecological/urogenital, musculoskeletal/extremities, skin, neurological/psychiatric, endocrine/metabolic, hematologic/lymphatic, allergies/drug sensitivities, past surgeries, substance abuse or any other diseases or disorders.

Any surgical as well as medication use history is to be recorded as well, including the time and type of the surgery received or medication taken.

7.5.5.4 Physical Examination

Physical examinations will be performed and any changes compared to the Screening assessment will be recorded as AEs.

The physical examinations will be performed by a physician and will include the examination of the following: general appearance, weight and height (at Screening), abdomen; head and neck; eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, neurological/psychiatric.

Additional examinations may be performed as part of the physical examination at Investigator's discretion for any AE related physical examinations if found necessary in the clinical judgment of the Investigator.

7.5.6 Other Assessments

Assessment times are included in the schedule of assessments (see Section 11.2).

7.5.6.1 Demographic and Other Baseline Characteristics

Demographic data (including date of birth, age, race, ethnicity, gender, and menopausal status) will be recorded at Screening.

All subjects will be asked about their disease history and significant medical history (including drug history, any surgical history, and family history).

7.5.6.2 Eastern Cooperative Oncology Group Performance Status

ECOG status will be ascertained by investigator /designee at screening and subsequent visits as noted in the schedule of assessments and at survival follow-up.

7.5.6.3 Tumor Response Assessment

A variety of tests are used to diagnose, determine disease phase, and monitor CML for example:

1. Complete blood count with differential for hematological response assessments.
2. Bone marrow aspiration for cytogenetic assessments.
3. Bone marrow biopsy will be used only in cases wherein the bone marrow aspiration was unsuccessful because the marrow is too fibrous to permit aspiration through the bone marrow biopsy needle.
4. Florescence in situ hybridization will be utilized for detection of minimum residual disease or in cases wherein enough sample was not available to conduct karyotyping

Serum, blood, and bone marrow-based samples will be collected at specified time points.

7.6 DATA COLLECTION DATA COLLECTION

A Code of Federal Regulations Title 21 Part 11-compliant EDC system will be used for this study. The eCRFs will be produced for each subject. The majority of study data collected will be either directly entered by the study center staff or directly captured from devices onto the eCRF. Data will be available for Sponsor review via predefined reports extracted from the database at agreed intervals. The eCRFs must be kept in order and up-to-date so that they reflect the latest observations on the enrolled subjects.

When direct data entry onto the eCRF is inappropriate or impractical data will be collected on paper source documents and subsequently transcribed, where necessary, onto the eCRFs by the study center staff. All source documents will be retained. Photocopies of completed source documents will be provided only if essential (i.e., for regulatory purposes) at the request of the Sponsor.

Safety laboratory data are managed and stored within the appropriate system and only the date and time of sampling will be recorded in the eCRF. Safety laboratory data will be integrated with the consolidated clinical data before database lock.

The informed consent will be kept with a copy of the completed source documents in the appropriate file folder provided, or a note to indicate where the records can be located. All records should be kept in conformance to applicable national laws and regulations.

Validity and consistency of data will be checked by employing pre-programmed data validation rules that will be applied to the data extracted from the EDC system during the

course of the study. The data management team will raise queries in the EDC system to resolve discrepancies. The Investigator must verify that all data entries in the eCRFs are accurate and correct. After completion of the study and when all collected data is validated, the database will be locked, pursuant to the prior approval by the Sponsor. Final data will be extracted from the EDC and delivered to the Sponsor in form of SAS[®] datasets. A portable document format copy of the eCRF will be produced for each study subject and included in the final delivery.

All eCRF entries, corrections, and alterations must be made by the Investigator or other, authorized, study center staff and only by individuals who have received training on the EDC system. Study center staff may be allowed access to the system only after the relevant training is completed. Training must be documented and a log of all EDC users and their rights within the system be maintained.

Adverse events will be coded using the current MedDRA dictionary; concomitant medications will be coded using World Health Organization's Drug Dictionary.

The EDC system will keep track of all data entry, alterations and query resolution in an audit trail. The audit trail will form an integral part of the database and will be archived alongside with the data.

7.7 EVALUATION OF STUDY DATA

7.7.1 Evaluation of Pharmacokinetic Parameters

Pharmacokinetic analysis will be performed [REDACTED]. The actual elapsed time from dose will be used in the final PK parameter calculations. Data handling, analysis procedures and data reporting will be detailed in the SAP.

Where possible, the following plasma PK parameters will be determined for K0706:

For Day 1 of Cycle 1 and Cycle 2

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

- [REDACTED]
[REDACTED]
[REDACTED]

Other parameters may be added as appropriate. The final PK parameters reported will be detailed in the SAP plan.

7.7.2 Evaluation of Efficacy

Efficacy will be determined by analysis of peripheral blood and bone marrow. Automated complete blood counts, differential counts (may include manual confirmation of abnormalities), physical examination, bone marrow differential, florescence in situ hybridization in case of minimum residual disease, RT-PCR and conventional cytogenetics [REDACTED] will be used to determine the response to treatment. Cytogenetic, molecular, and hematologic response will be estimated for all subjects. The timing of these assessments will be according to the schedule of assessments, Section 11.2.

Molecular response monitoring using PCR for BCR-ABL copy number will be performed on peripheral blood and will be sent to for assessment on the international scale.

Automated complete blood counts and differential counts (with manual confirmation of abnormalities), [REDACTED] will be used to determine response to treatment. CHR will be evaluated by peripheral blood utilizing local laboratory results. The local laboratory reference ranges will be included in the EDC. The local laboratory may be requested to perform manual confirmation of abnormalities using peripheral blood smears. In this case at least 3 separate smears prepared from the same sample should be read before reporting the results.

Bone marrow samples (i.e.: Bone marrow aspirates) will be evaluated for review of cytogenetics and florescence in situ hybridization (FISH). [REDACTED]
[REDACTED]
[REDACTED]

Please see the Laboratory Manual for processing and shipping of samples.

Bone marrow aspirates will be performed as part of screening for the study. If bone marrow aspirates at screening yield an invalid result, the bone marrow aspiration will be repeated to have evaluable result prior to study drug administration on Cycle 1 Day1. Subject will be dosed upon confirmation of valid bone marrow evaluation outcome. In case of a repeat in bone marrow, screening period will be extended.

Standard cytogenetics will be used to determine the presence of the Ph⁺ and its presence (percentage) in the bone marrow aspirates. The Investigator must ensure that the

pathology laboratory and/or pathologist performing the cytogenetic and fluorescence in situ hybridization analysis is blinded to treatment information and is trained in performing the procedure under appropriate aseptic conditions. Documentation of subject's treatment information cannot be contained in any request forms or directives for sample processing.

Fluorescence in situ hybridization analysis (performed on bone marrow) will also be used to confirm presence of BCR-ABL fusion product in case of subjects who have achieved complete cytogenetic response with study drug or have minimum residual disease.

Bone marrow cell differential will also be used to determine the blast and immature myeloid counts and cellularity if required.

Physical examination will be used to assess hepatic and spleen involvement.

To understand the exploratory objectives:

In the study, serum, blood, and bone marrow-based samples will be collected at specified time points to determine the following:

- BCR-ABL mutation profile at screening
- BCR-ABL mutation profile at progression (should it occur)


Samples for BCR-ABL mutation profiles will be performed during Screening and at progression if observed. Additional efficacy parameters may be evaluated and will be detailed in the statistical analysis plan.

7.7.3 Evaluation of Safety

The safety and tolerability profile of K0706 in subjects treated on this study will be assessed by physical examination, AEs, vital signs (including blood pressure [systolic and diastolic], pulse rate, respiratory rate, and temperature), ECG, and clinical laboratory tests (including hematology, coagulation, cardiac troponin, clinical chemistry, and urinalysis). The timing of these assessments will be according to the schedule of assessments Section 11.2

Adverse events will be assessed based on the NCI CTCAE v5.0 and categorized as SAEs or AEs. The relationship of AEs to K0706 will be assessed by the Investigator per the protocol-defined criteria for attribution assessment.

Subject performance status will be assessed using the ECOG performance status scale.

Subject survival will be followed every  months (± 2 weeks) by telephone contact, medical record review, and/or study center visits wherein information about subject survival and anticancer therapies will be collected after the end of treatment until death, withdrawal of consent, or the end of the study, whichever comes first.

7.8 STATISTICAL METHODS

In general, descriptive summaries will be presented for the safety and efficacy variables collected. Continuous variables will be summarized [REDACTED]. Categorical variables will be summarized [REDACTED]. For time-to-event variables, [REDACTED] will be presented.

Adverse events will be coded using MedDRA and will be summarized by System Organ Class and Preferred Term. In addition, summaries of AEs by severity and relationship to K0706 will be presented.

Formal testing of treatment effects will not be performed. However, where appropriate, some measures will be summarized by both point estimates and estimation of 95% confidence intervals. More detailed information about estimation of treatment effects, summarization of data, graphical representations, and analysis conventions will be provided in the SAP.

7.8.1 Primary and Secondary Target Variables

Primary Endpoints

- Cohort A: For CML subjects in CP at study entry: major cytogenetic response (MCyR), defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR). (CP subjects in CCyR are not eligible for this study)
For subjects entering the study in PCyR, achieving CCyR on the study drug will be considered as MCyR.
- Cohort B: For CML subjects in AP at study entry: major hematologic response (MaHR), defined as complete hematologic response (CHR) or no evidence of leukemia (NEL). (AP subjects in MaHR are not eligible for this study)
- Cohort C : For CML subjects in BP : MaHR, consisting of CHR
Or NEL. (BP subjects in MaHR are not eligible for this study)

Secondary Endpoints

- In subjects with CML-CP
 - Hematological responses: Proportion of subjects who develop complete hematological response
 - Cytogenetic responses: Proportion of subjects who develop CCyR
 - Molecular responses: Proportion of subjects who achieve MMR
- In subjects with CML-AP or CML-BP

- Cytogenetic responses: Proportion of subjects who achieve CCyR or PCyR,
- Molecular responses: Proportion of subjects who achieve MMR
- In all subjects: Safety and tolerability in terms of incidence and severity of treatment emergent AEs
- In all subjects: Time to response, duration of response, progression free survival and overall survival

Table 7-13 Efficacy Assessment of Primary End points

| | Cohort A | | Cohort B and C ^a |
|-------------------------------|---|--|---|
| Primary endpoint will include | Subjects entering the study with less than PCyR | Unconfirmed MCyR: That is detection of a complete or partial cytogenetic response on a single bone marrow aspirate will qualify as a response for determination of efficacy. | Confirmed MaHR: This includes demonstration of CHR or NEL confirmed by 2 hematological assessments performed at least 4 weeks apart. The hematological assessments will include a peripheral blood CBC and differential to qualify as a response. |
| | Subjects entering the study with PCyR | Unconfirmed CCyR: That is detection of Complete cytogenetic response on a single bone marrow aspirate will qualify as a response for determination of efficacy. | |

a: Criteria for responses are included in Appendix 1

7.8.2 Sample Size Determination

Cohort A (CML-CP) may enroll up to approximately [REDACTED] subjects at [REDACTED] mg, which accounts for up to a [REDACTED] dropout rate, with the goal of achieving [REDACTED] evaluable subjects. This sample size is based on studies where subjects had failed more than two lines of therapy, including a trial for Omacetaxine (NDA 203585; US FDA CDER Medical Review, 02 Sep 2012) and other studies with failure to both dasatinib and nilotinib where MCyR response rates ranging from 11.1% to 30% were seen [REDACTED]. With a null response rate ([REDACTED] lower CI bound) of [REDACTED] and an alternative response rate ([REDACTED] upper CI bound) of [REDACTED], [REDACTED] subjects will provide [REDACTED] power at an overall alpha of [REDACTED]. A minimum of [REDACTED] responders ([REDACTED] are needed to observe an exact [REDACTED] CI exceeding the lower bound of [REDACTED] and an upper bound of [REDACTED].

Both Cohorts B (CML-AP) and C (CML-BP) may enroll up to approximately [REDACTED] subjects each at [REDACTED] mg, which accounts for up to a [REDACTED] dropout rate, with the goal of achieving [REDACTED] evaluable subjects. With a null response rate ([REDACTED] lower CI bound) of [REDACTED] and an

alternative response rate ([REDACTED] upper CI bound) of [REDACTED] subjects will provide [REDACTED] power at an overall alpha of [REDACTED]. A minimum of [REDACTED] responders ([REDACTED] are needed to observe an exact [REDACTED] CI exceeding the lower bound of [REDACTED] and an upper bound of [REDACTED]. An assumed treatment response rate of [REDACTED] is based, approximately, on results for MaHR in CML-AP for Omacetaxine (TEVA Pharmaceutical Industries, Ltd.), in this patient population (actual rate: 20.8% [5/24]), as presented in NDA 203585 (US FDA CDER Medical Review, 02Sep2012).

Power and sample size for each Cohort were calculated based on a test for one proportion, using a [REDACTED] to the binomial distribution with standard deviation based on $P\text{-hat}$ with continuity correction, assuming a [REDACTED].

For Cohorts A, B, and C, response rates will be monitored in an ongoing manner to determine if they are below the assumed null response rates, in order to use this information in parallel with DLT rates and other internal DSMB safety monitoring to assess for futility, thereby further protecting subject safety.

7.8.3 Subject Population for Analyses

7.8.3.1 Safety Analysis Set

The safety analysis set will include all subjects who receive at least 1 administration of IMP.

7.8.3.2 Efficacy analysis set.

The efficacy analysis set will be:

Cohort A, B and C: Include subjects who have had at least one K0706 dosing.

Each of these cohorts will be assessed separately for efficacy and safety. Efficacy analysis from subjects enrolled at [REDACTED] mg will be presented separately.

7.8.3.3 Pharmacokinetic Analysis Set

The PK analysis set will include all subjects who receive at least 1 dose of K0706 and have at least 1 measured K0706 plasma concentration at a scheduled PK time point postdose with no important protocol deviations, violations, or events thought to significantly affect the PK of the drug.

7.8.4 Pharmacokinetic Analysis

7.8.4.1 Statistical Analysis of Pharmacokinetics

Plasma concentrations and PK parameters for K0706 will be listed and summarized. Any additional PK evaluations or illustrations will be described in the SAP.

7.8.5 Efficacy Analysis

All efficacy analysis will be performed separately per Cohort (designated from Cohort A to C), and will include all subjects in the efficacy analysis set enrolled. Primary and

secondary efficacy response rates will be summarized by both point estimates and estimation of [REDACTED] confidence intervals. Detailed information for censoring rules for PFS and OS will be incorporated in the SAP. More detailed information about estimation of treatment effects, summarization of data, graphical representations, and analysis conventions will be provided in the SAP.

7.8.6 Subject Disposition

Subjects will be summarized as per the disease Cohort (i.e.: Cohorts A, B or C).

Subjects receiving treatment will be presented. Subjects receiving treatment who are found not to have fully met the eligibility criteria will be presented. On-study protocol violations will also be presented. Subjects who do not complete the required observations will be listed and evaluated separately as necessary. Study completion rates by Cohort, and reasons for study discontinuation will be summarized. Numbers of subjects enrolled in each analysis population will be presented.

7.8.7 Subject Characteristics

All baseline and demographic variables will be summarized descriptively, using [REDACTED]. The results will be presented in summary tables and by-patient listings. Baseline disease characteristics will be presented descriptively.

7.8.8 Exploratory Analysis

Continuous PD endpoints will be summarized by dose cohort and/or disease subsets or disease cohorts and scheduled visit by descriptive statistics [REDACTED]. Categorical endpoints will be summarized by proportion in each category by dose cohort and scheduled visit.

Any additional PD evaluations will be described in the SAP.

7.8.9 Safety Data Analysis

Individual and summary blood pressures, heart rate, ECG parameters and clinical laboratory data will be presented in tabular form [REDACTED] as appropriate. The data will be summarized by dose cohort and scheduled visit. Unscheduled data will not be included in the summary tables, but will be included in the listings.

For the laboratory safety data, out of range values will be flagged in the data listings and a list of clinically significantly abnormal values will be presented.

Adverse events will be tabulated and summarized according to the current version of MedDRA. AEs will be summarized according to dose and disease cohorts.

7.8.10 Data Safety Monitoring Board

A DSMB will be established for periodic review of safety data for this study. The composition and responsibilities of the DSMB will be described in detail within the DSMB Charter for this study Section 8.5.

7.9 STUDY REPORT

A clinical study report, compliant with the requirements of ICH E3, will be prepared [REDACTED]

[REDACTED]

8 REGULATORY AND ETHICAL ISSUES: PARTS B & C

8.1 Regulatory and Ethics Review and Approval

This study is to be conducted according to globally accepted standards of GCP (as defined in the ICH E6 Guideline for GCP), in agreement with the latest revision of the Declaration of Helsinki and in keeping with local regulations. Before initiation of the study, approvals from the applicable Regulatory Authority(ies) will be obtained. The Investigator must obtain approval or favorable opinion of the protocol, ICF and any advertisement for subject recruitment from the Ethics Committee complying with the applicable pertinent government regulations. The Ethics Committee will evaluate the ethical, scientific and medical appropriateness of the study.

The documents submitted will include but are not limited to the final protocol, the IB, the ethics application form, and the ICF.

The study will not commence unless the following conditions are satisfied:

An Ethics Committee has given a favorable opinion in relation to the clinical study; and
The clinical study has been authorized by the licensing authority

8.2 Subject Information and Informed Consent

Before any study-related activities are carried out such as Screening and enrolment, each prospective candidate will be given a full explanation of the study, allowed to read the approved ICF in a local language and will be provided ample time and opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the individual understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing and personally dating the ICF. The Investigator will provide a copy of the signed and dated ICF to each subject.

The nature of the ICF will comply with the current version of the Declaration of Helsinki, the current requirements of GCP and local regulations, which ever provides the greater subject protection.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the ICF must be revised and submitted to an Ethics Committee for review and approval or favorable opinion. The revised ICF must be used to obtain consent from any subject currently enrolled in the study if he is affected by the amendment. The revised ICF must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the amendment by the Ethics Committee.

The signed and dated declaration of informed consent will remain at the Investigator's study center, and must be safely archived by the Investigator so that the ICFs can be retrieved at any time for monitoring, auditing, and inspection purposes.

8.3 Statement of Confidentiality

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under the appropriate patient number. Only the Investigator will be able to link trial data to an individual subject via an identification list kept at the site. Once the trial has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, for each subject, original medical data will be accessible for the purposes of source data verification by the monitor, audits and regulatory inspections (eg, FDA, EMA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs but patient confidentiality will be maintained. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

The results of studies, containing subjects' unique identifying number, will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

8.4 Indemnity and Compensation

The Sponsor will indemnify the Investigators from all and any claims arising out of this study except for their negligence or malpractice and providing that the study is conducted according to the standards established by the protocol.

In the event that it can be demonstrated that a subject suffers any significant deterioration in health or well-being or any harmful susceptibility or toxicity as a direct result of their participation in this study then the Sponsor will agree to abide by the current FDA guidelines, as well as any local regulations that may apply, with regard to compensation payable to the subject. The amount of compensation will be calculated by reference to the level of damages commonly awarded in law for similar injuries at the time when such an injury occurred.

The Investigators declare to having insurance cover for the malpractice and/or negligence of their employees and age.

8.5 Data Safety Monitoring Board

An independent DSMB will be established to periodically review safety results of Pivotal Part C study. The DSMB will have access to study data. Based on the results of the interim review the DSMB will submit its recommendations in written form to the Sponsor who is responsible for responding to the recommendations of the DSMB and to take appropriate action. The Investigators will only be informed by the Sponsor in case of stopping the study. The DSMB may choose to request additional evaluations at any time if they feel this is warranted from the standpoint of safety.

The DSMB will act according to its own written SOP described in a charter and will prepare written minutes of its meetings. In order not to disseminate the data only the members of the DSMB and the statistician will have access to these data. The results will be sent confidentially to the DSMB by the statistician.

9 STUDY MANAGEMENT: PARTS B & C

9.1 Quality Assurance and Quality Control

In accordance with the guideline for ICH GCP, the Sponsor has responsibility for implementing and maintaining quality assurance and quality control systems, and the ultimate responsibility for the quality integrity of the study data resides with the Sponsor.

Data will be captured in a standardized format according to the study center's standard operating procedures and those procedures specified in the study documentation.

A Code of Federal Regulations Title 21, Part 11-compliant EDC system will be used for this study. The eCRFs will be produced for each subject. Where eCRFs are not possible, the source data will be captured on paper.

The Investigator will ensure the accuracy, completeness and timeliness of the data recorded for data queries and all required reports according to any instructions provided.

9.2 Protocol Adherence

The protocol must be read thoroughly and the instructions followed exactly. Any deviations should be agreed by both the Sponsor and the Investigator, with the appropriate written and approved protocol amendments made to reflect the changes agreed upon. Where the deviation occurs for the well-being of the subject, the Sponsor must be informed of the action agreed upon.

9.3 Documents Necessary for Initiation of Study

For the documents necessary for initiation of study please refer to applicable regulatory and GCP requirements for the country.

9.4 Study Monitoring

This study will be monitored in accordance with the ICH GCP. The clinical monitor, whether an employee of the Sponsor or its designated representative, has the obligation to follow this study closely. In doing so, the clinical monitor will visit the clinical study center at periodic intervals, in addition to maintaining necessary telephone and letter contact. The clinical monitor will monitor current personal knowledge of the study through observation, review of study records and source documentation and discussion of the conduct of the study with the Investigator and study center staff. Quality assurance auditors, whether employees of the Sponsor or its designated representative, may evaluate the conduct of the study by the study center at any time during or after the study to ensure the validity and integrity of the study data. These parties must have access to all study reports and source documentation, regardless of location and format.

Upon completion of the study, the clinical monitor will arrange for a final review of the study files, after which the files should be secured for the appropriate time. The Investigator, or appointed delegate, will meet with the monitor during the on-site visits and will co-operate in providing the documents for inspection and respond to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of the Sponsor or the regulatory agencies.

The Investigator will allow study-related monitoring audits, Ethics Committee and regulatory inspections allowing direct access to study-related source data/documents.

9.5 Study Closure

The Investigator reserves the right to terminate the study in the interest of subject welfare.

The Sponsor may terminate the study at any time.

Premature termination of the study by any party will be governed under the terms of the contract between the parties and the prevailing safety and well-being of subjects.

The end of the study is defined as 'the last visit of the last subject in the study'. This would be the last follow-up of the last subject, however, the study may be concluded earlier if required by the Sponsor.

9.6 Study Record Retention

The Sponsor and the Principal Investigator shall ensure that the documents contained, or which have been contained, in the Trial Master File are retained for at least 15 years after the conclusion of the study and that during that period are:

Readily available to the licensing authority on request; and Complete and legible.

All data derived from the study will remain the property of SPARC. The study will be the subject of a final clinical study report compiled by, or by order of SPARC.

All correspondence (e.g., with the Sponsor, Ethics Committee) relating to this study should be kept in the appropriate file folders.

Records of subjects source documents, eCRF's, IMP inventory, pertaining to the study must be kept on file. Records must be retained according to the current ICH Guidelines on GCP.

The Sponsor and Principal Investigator shall ensure that the medical files of study subjects are retained for at least 15 years after the conclusion of the study. The Sponsor shall appoint named individuals within his organization to be responsible for archiving the documents which are, or have been, contained in the Trial Master File. Access to those documents shall be restricted to those appointed individuals. If there is transfer of ownership of data or documents connected with the clinical study:

The Sponsor shall record the transfer; and the new owner shall be responsible for data retention and archiving

If the Investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

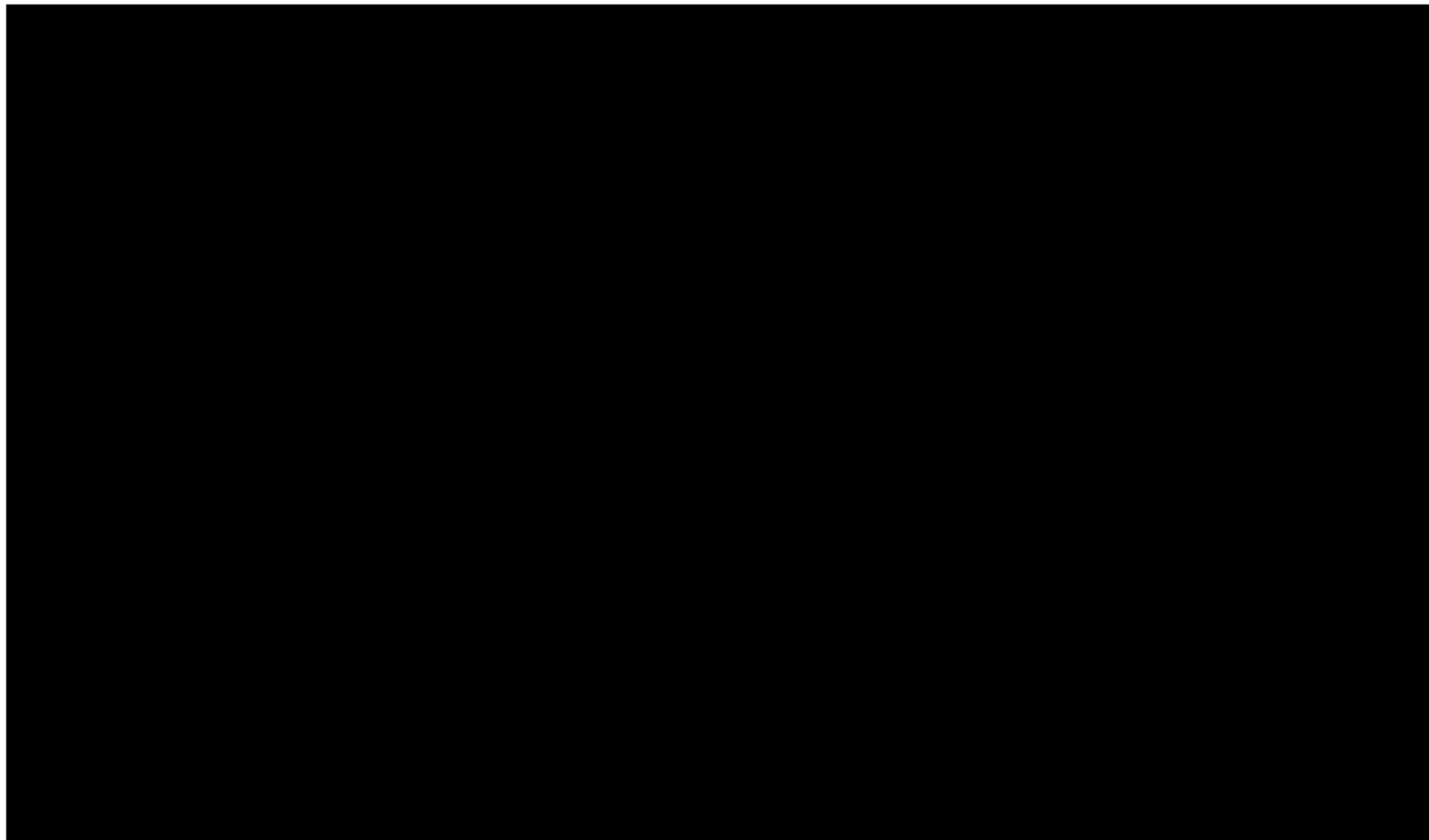
9.7 Publication Policy

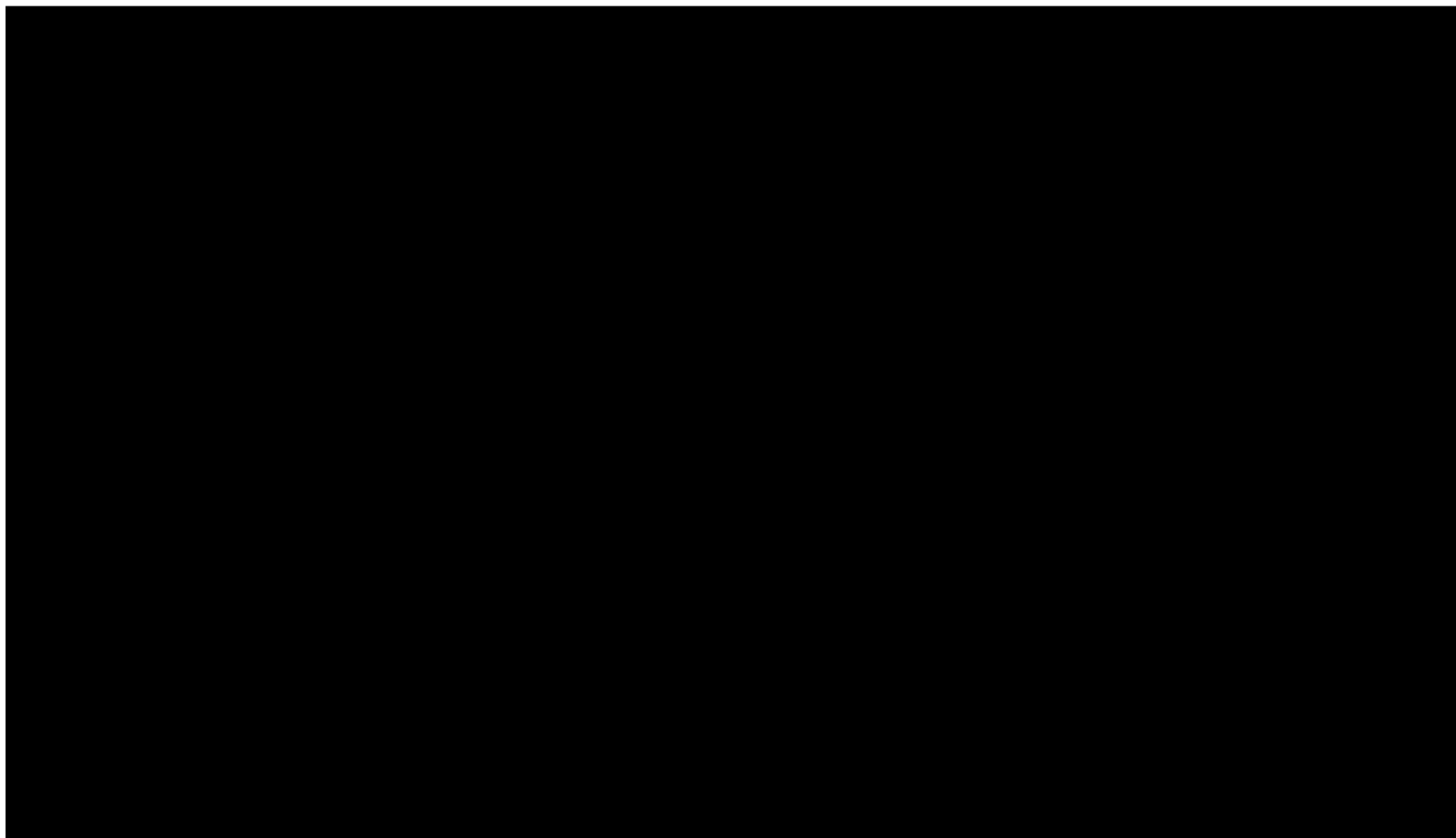
After completion of the study, the Investigator may prepare a joint publication with the Sponsor. The Investigator must undertake not to submit any part of the individual data from this protocol for publication without prior consent of the Sponsor at a mutually agreed time.

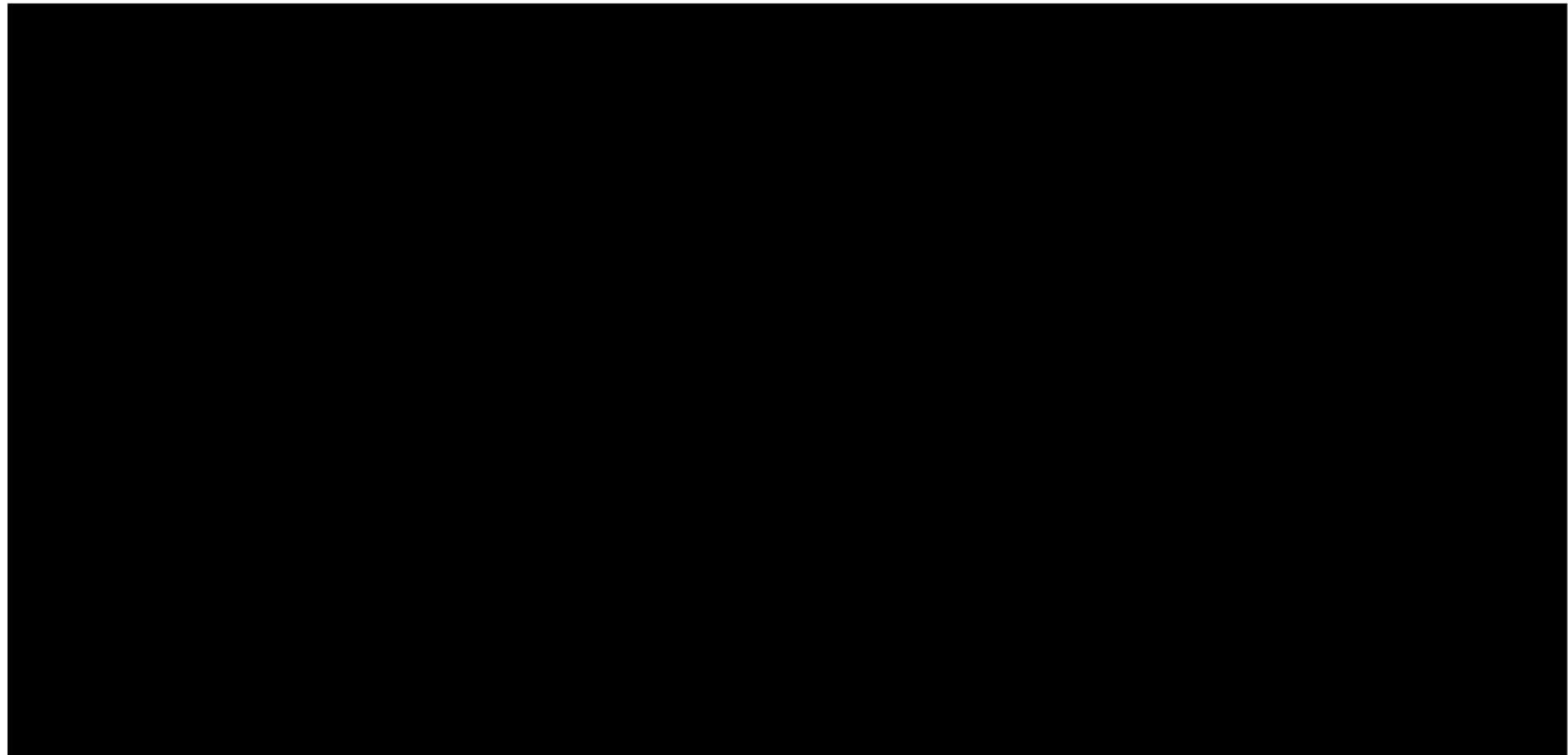
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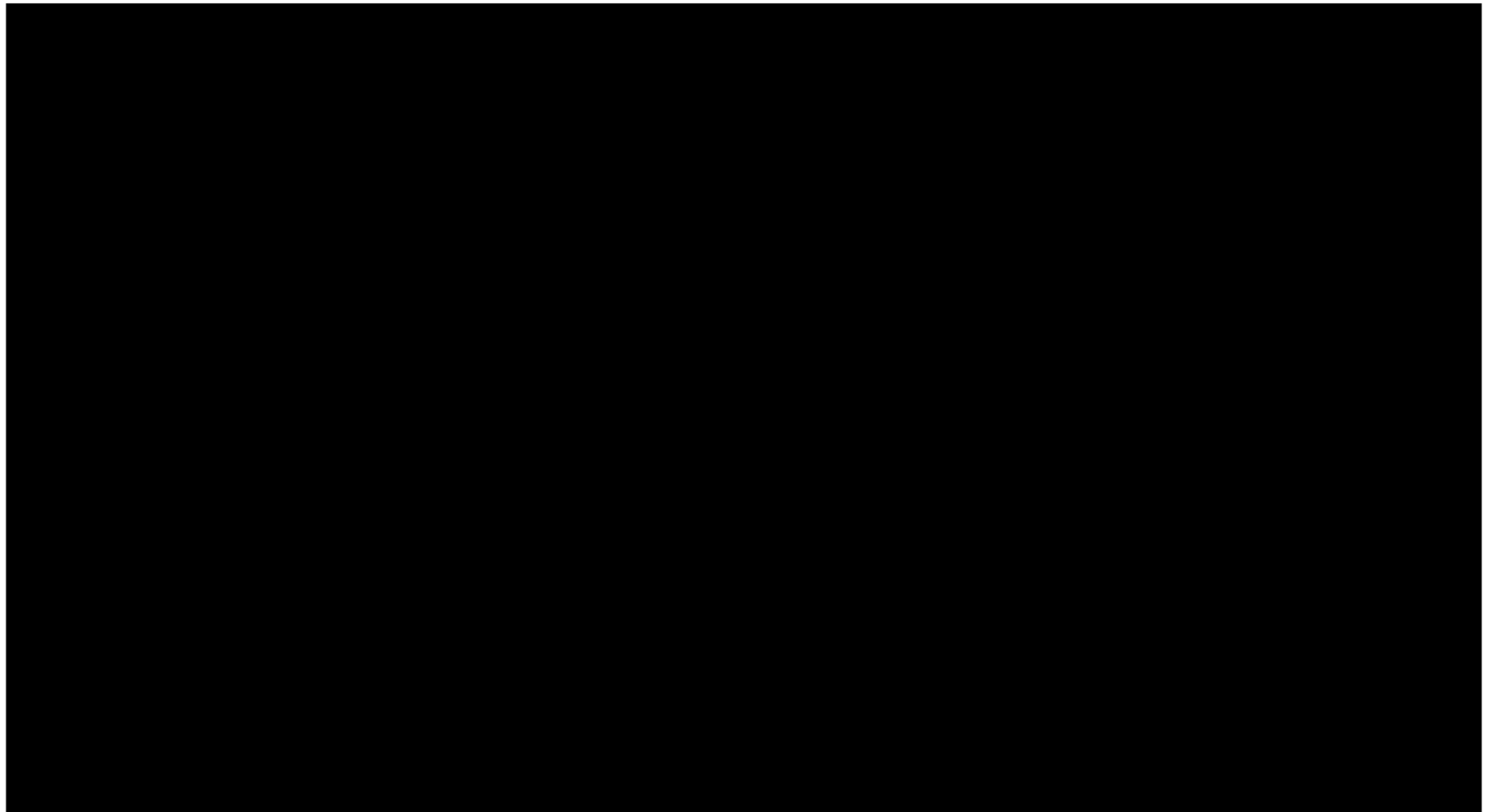
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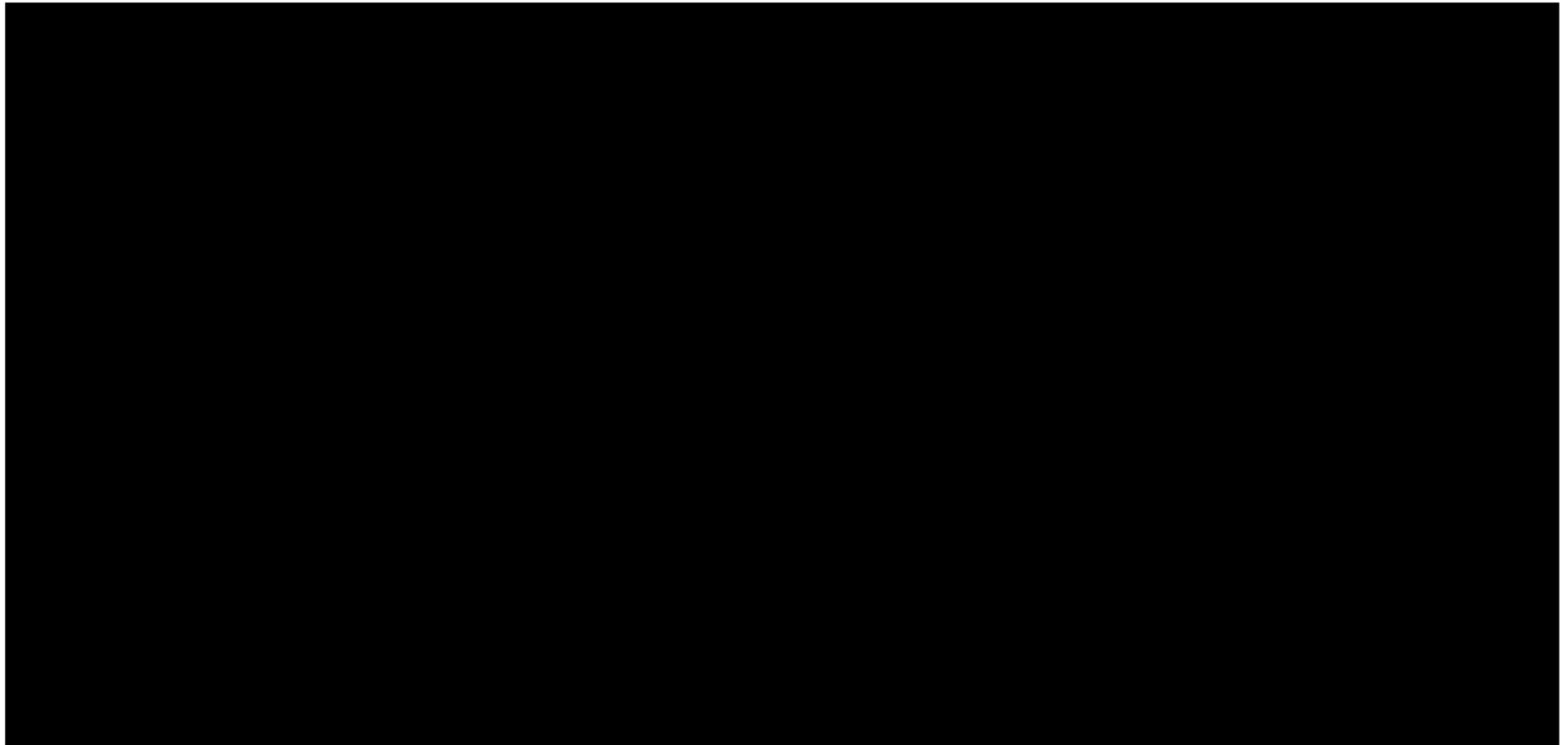
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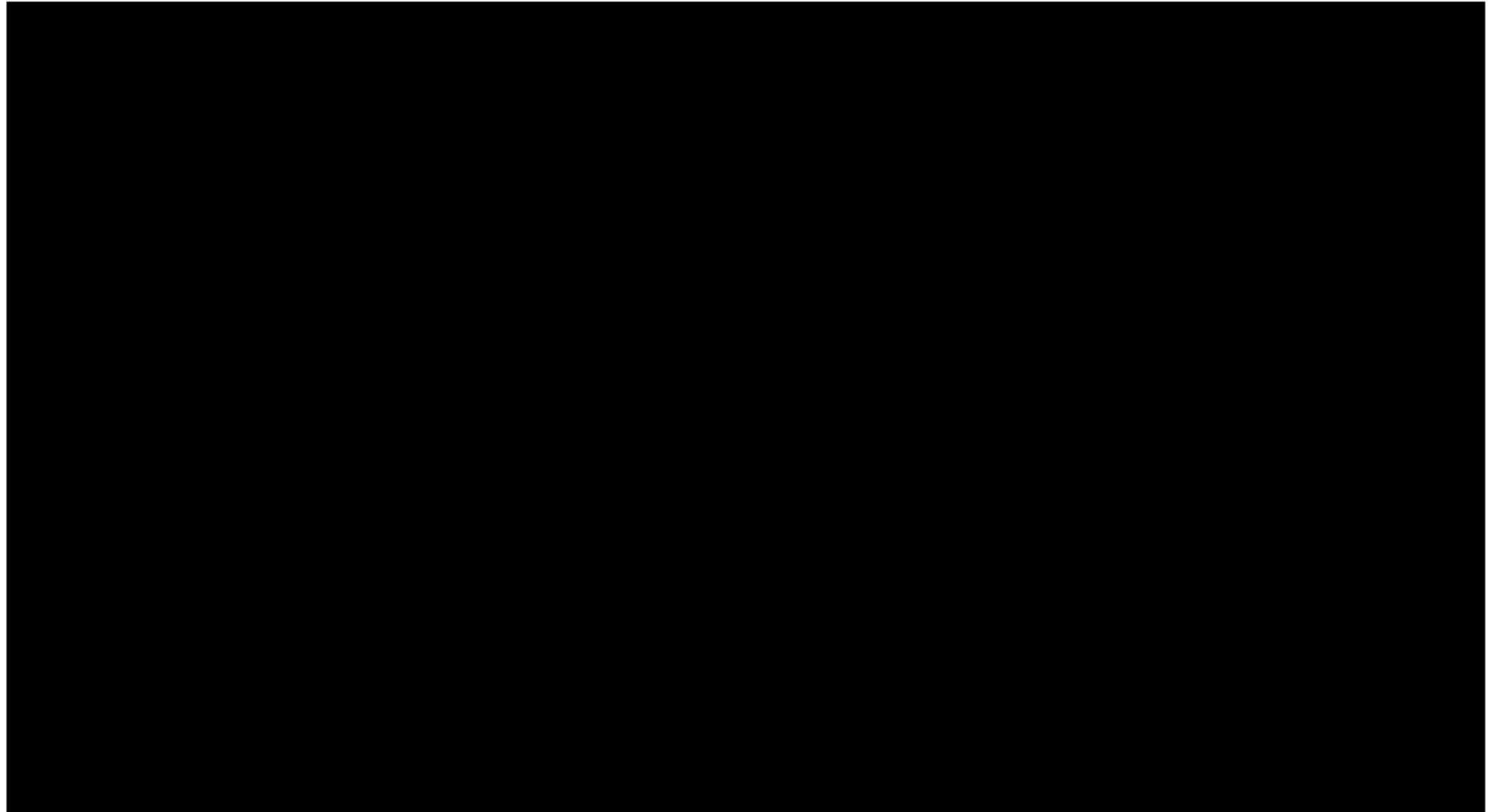


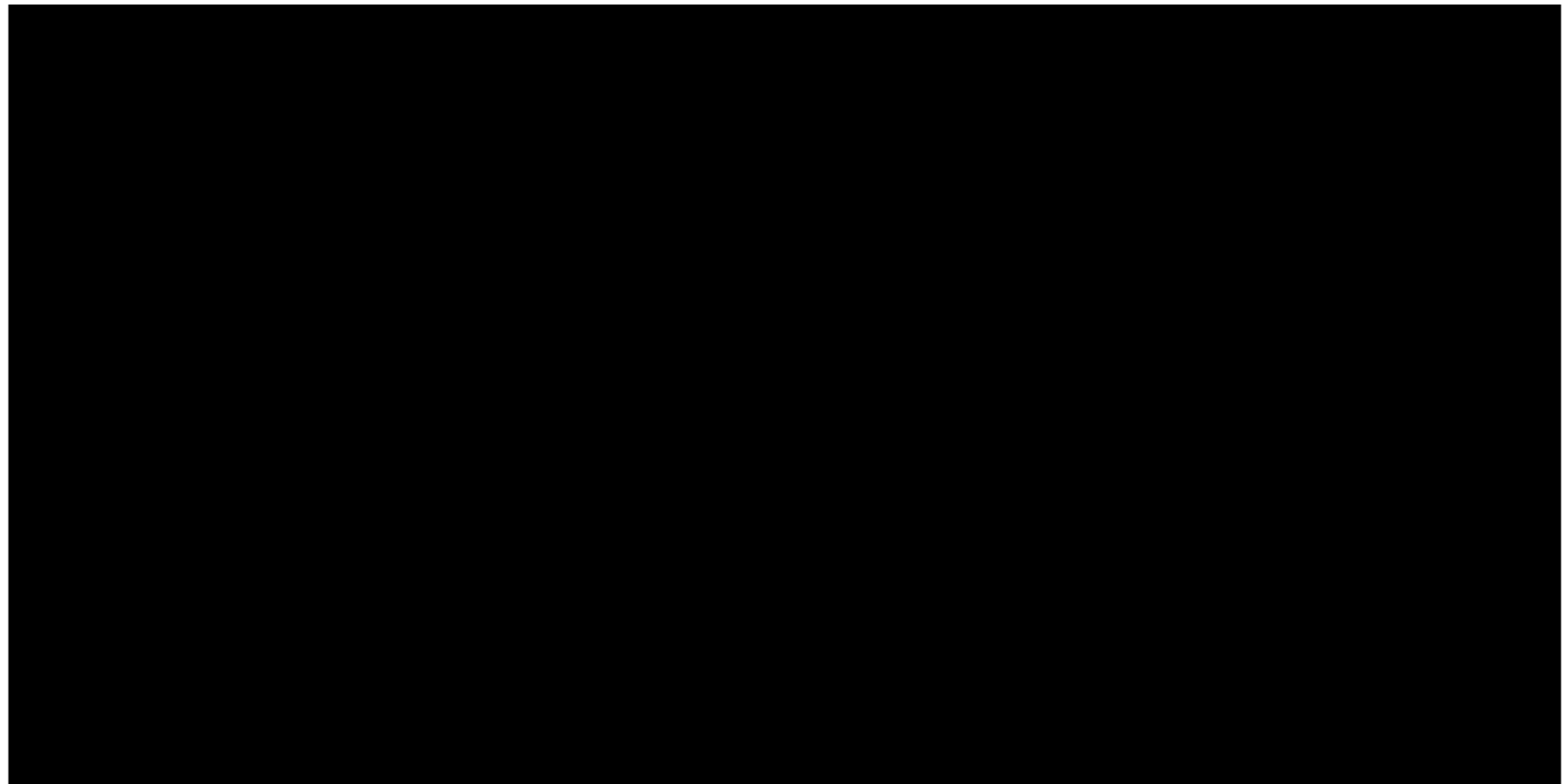


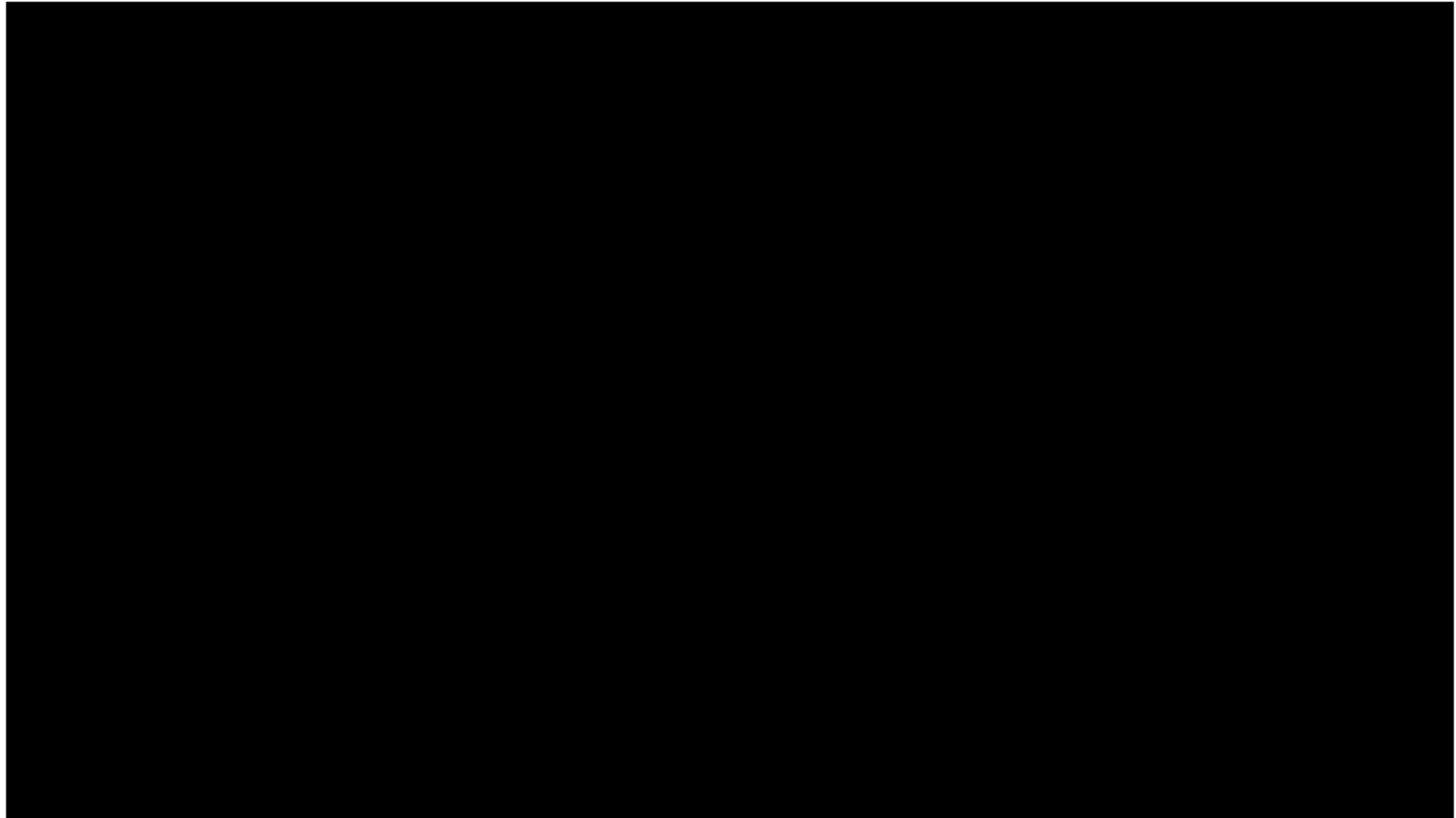


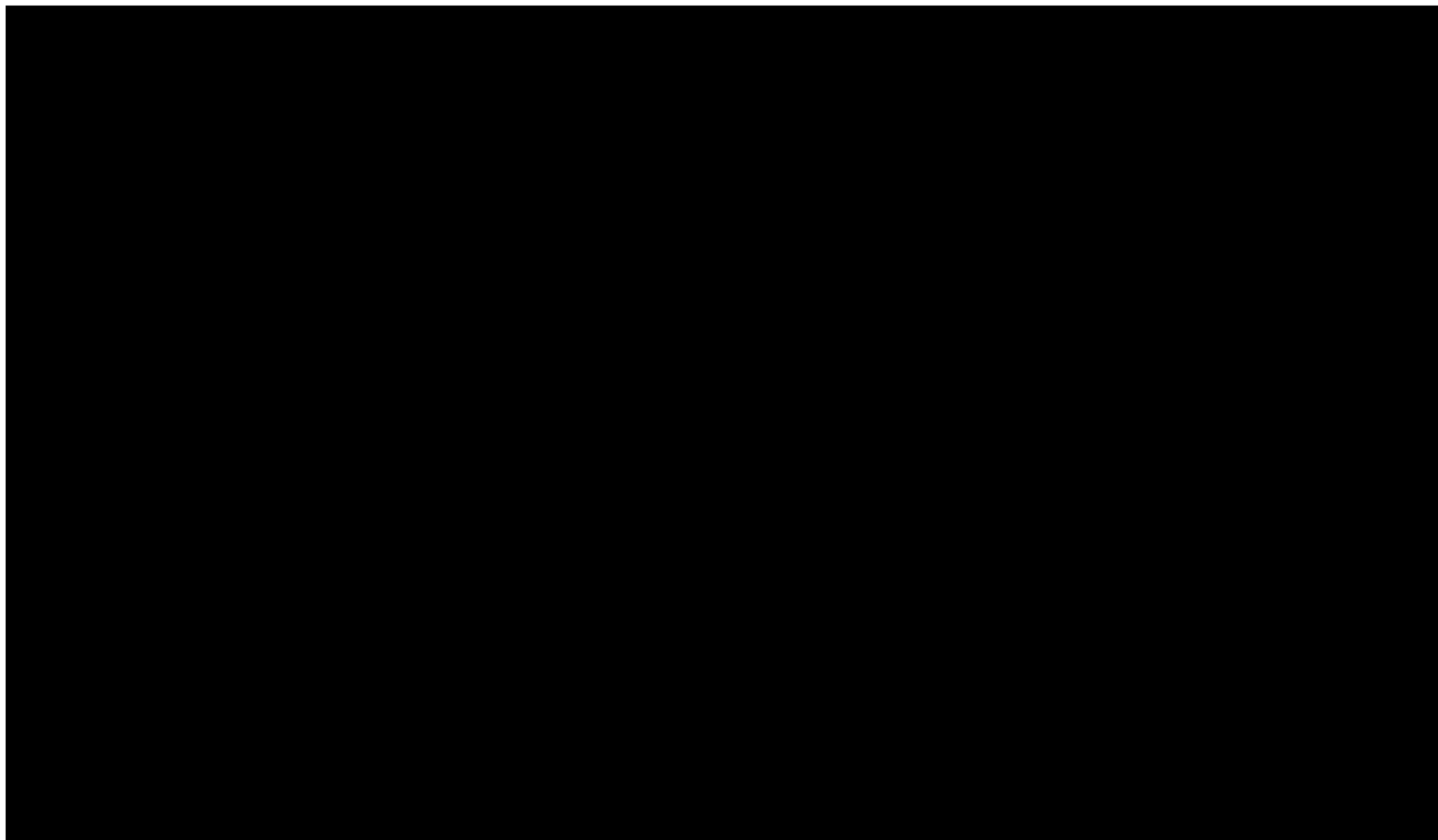


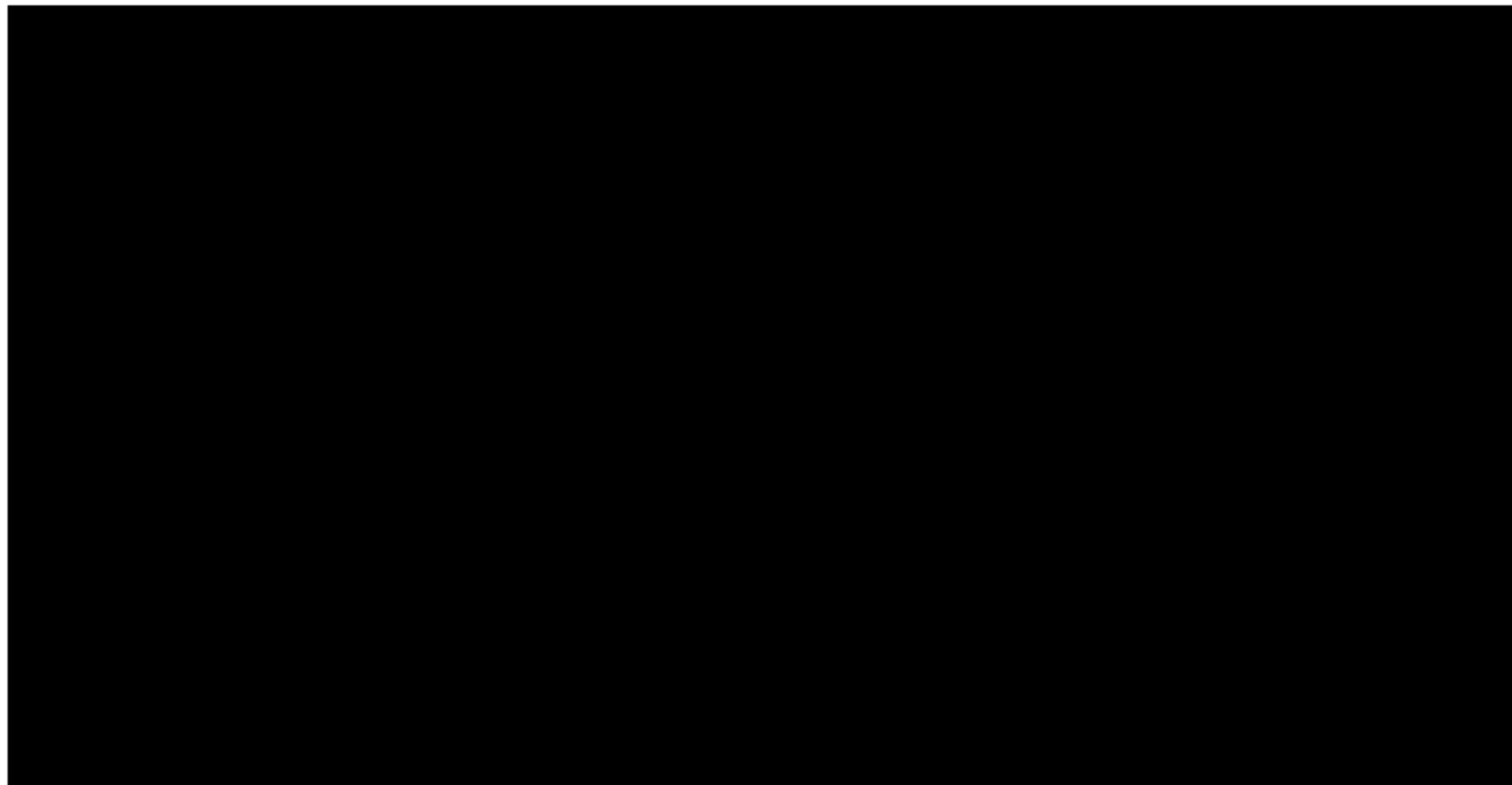












12 PROTOCOL SIGNATURES

SPONSOR SIGNATURE:

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Investigator has the right to discontinue the study at any time. I have read the protocol and understand it and will ensure that the clinical study is conducted according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

[REDACTED]

13 APPENDIX

13.1 APPENDIX I

CRITERIA FOR RESPONSE

Haematological response

Major haematological response (MaHR) is inclusive of complete haematological response (CHR) and/or no evidence of leukemia (NEL).

For subjects who enter the study in MaHR response, the criteria for evaluating response is: Maintenance of MaHR for upto 12 weeks after initiation of study treatment.

These criteria are adapted from Talpaz et al., 2006, O'Brien et al., 2003, and Kantarjian et al., 2010.

| Haematological response criteria for Subjects with CML-AP and CML-BP and Ph+ ALL | |
|--|---|
| CHR | <ul style="list-style-type: none"> • White blood cells (WBCs) \leq Institutional upper limit of normal • $ANC \geq 1000/mm^3$ • Platelets $\geq 100,000/m^3$ • No blasts or promyelocytes in peripheral blood • $< 5\%$ basophils on differential • $< 5\%$ myelocytes and metamyelocytes on peripheral blood • No extra-medullary involvement (no hepatomegaly and/or splenomegaly) |
| NEL | <p>White blood cells (WBCs) \leq Institutional upper limit of normal</p> <p>No blasts or promyelocytes in peripheral blood</p> <p>$< 5\%$ basophils on differential</p> <p>$< 5\%$ myelocytes and metamyelocytes on peripheral blood</p> <p>No extra-medullary involvement (no hepatomegaly and/or splenomegaly)</p> <p>At least one of the following</p> <ul style="list-style-type: none"> • $20,000/mm^3 \leq Platelets \leq 100,000/mm^3$ • $500/mm^3 \leq ANC \leq 1000/mm^3$ |

| Complete haematological response (CHR) for Subjects with CML-CP | |
|---|--|
| CHR | <p>Platelets $< 450 \times 10^9/mm^3$</p> <p>White blood cells (WBCs) \leq Institutional upper limit of normal</p> <p>No blasts or promyelocytes in peripheral blood</p> <p>$< 5\%$ basophils on differential</p> |

| | |
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| | < 5 % myelocytes and metamyelocytes on peripheral blood No extra-medullary involvement (no hepatomegaly and/or splenomegaly) |
|--|---|

Cytogenetic response:

Criteria for Cytogenetic response have been derived from Kantarjian et al, 2006, Talpaz et al, 2006 and National Comprehensive Cancer Network (NCCN), Clinical practice guidelines (2018).

At least 20 metaphase should be evaluated. If fewer metaphases are reported, absolute percentage values should be reported. Peripheral blood cells must not be used.

| Major Response | Cytogenetic Response | Complete (CCyR) | No Ph+ Cells |
|------------------|----------------------|-------------------------|--------------------|
| | | Partial Response (PCyR) | 1-35 % Ph+ Cells |
| Minor Response | | | 36-65 % Ph+ Cells |
| Minimal Response | | | 66-95 % Ph+ Cells |
| No Response | | | 96-100 % Ph+ Cells |

Under limited bone marrow aspirate availability precluding cytogenetic evaluation by Giemsa staining, FISH assay for evaluation of Ph+ Cells will be performed. A CcyR is reported for FISH when No Ph+ cells* are observed or fewer than 1 out of 200 nuclei BCR-ABL1-positive by FISH.

Major Molecular Response:

A major molecular response (MMR), is defined as a ratio of reverse transcribed transcript of BCR-ABL to ABL ≤ 0.1 % on the international scale (IS) (equivalent to 3 log reduction in transcript) (Baccarani et al., 2009).

13.2 APPENDIX II

Anticipated AEs and the risk monitoring methods in the study

| Anticipated AE | Risk Monitoring | Risk Monitoring Measures |
|-----------------|---|---|
| Fluid retention | Monitor subjects for development of signs and symptoms of fluid retention during clinical trial | Information included in the ICF for patient education, Included in the schedule of assessments in the Protocol: Intensive subject monitoring inclusive of physical examination, ECG, biochemistry. If AEs of fluid retention are suspected or detected, the subjects should also be monitored for signs and symptoms and management using supportive therapy may be considered according to standard medical practice, institutional and applicable protocol-specific guidelines. |

| | | |
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| Myelosuppression | Monitor complete blood counts regularly. | <p>Information included in the ICF for patient education</p> <p>Included in the schedule of assessments in the Protocol:</p> <p>Intensive haematology monitoring included in Cycle 1 and 2 at weekly intervals</p> <p>Additional haematology monitoring will be at Investigator's discretion based on subject's clinical condition and standard medical practice, institutional and applicable protocol-specific guidelines.</p> |
| Cardiac arrhythmias | <p>Monitor subject's vitals, BP, ECG regularly per protocol schedule of assessment</p> <p>Subjects should be advised to report signs and symptoms of slow or rapid heart rate</p> | <p>Information included in the ICF for patient education</p> <p>Included in the schedule of assessments in the Protocol:</p> <p>Intensive ECG monitoring included in Cycle 1 and 2 at weekly intervals and thereafter at every 3 monthly study visit</p> <p>Additional ECG and conduct of specific cardiac evaluations such as 2D echocardiography will be at Investigator's discretion based on subject's clinical condition and standard medical practice, institutional and applicable protocol-specific guidelines</p> <p>Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided as per protocol guidance</p> <p>Caution is recommended when administering to subjects with hepatic impairment.</p> |
| Heart failure | Subjects should be monitored for signs or symptoms consistent with cardiac dysfunction and should be treated appropriately. | See methods included in Cardiac arrhythmias above |
| Hepatotoxicity | Subject should be monitored for signs or symptoms consistent with hepatic dysfunction | <p>Information included in the ICF for patient education</p> <p>Included in the schedule of assessments in the Protocol:</p> <p>Intensive liver function tests (LFTs) and amylase monitoring included in Cycle 1 and 2 at weekly intervals and thereafter at every 3 monthly study visit</p> <p>Additional LFTs, biochemistry tests and conduct of specific evaluations such as USG abdomen, relevant viral markers will be at Investigator's discretion based on subject's clinical</p> |

| | | |
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| | | <p>condition and standard medical practice, institutional and applicable protocol-specific guidelines</p> <p>Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided as per protocol guidance</p> <p>Caution is recommended when administering to subjects with hepatic impairment.</p> |
| Pancreatitis | <p>Subject should be monitored for signs or symptoms consistent with pancreatic dysfunction</p> | <p>Information included in the ICF for patient education</p> <p>Included in the schedule of assessments in the Protocol:</p> <p>Intensive amylase monitoring included in Cycle 1 and 2 at weekly intervals and thereafter at every 3 monthly study visit</p> <p>Additional amylase, biochemistry tests and conduct of specific evaluations such as USG abdomen, relevant viral markers will be at Investigator's discretion based on subject's clinical condition and standard medical practice, institutional and applicable protocol-specific guidelines</p> <p>Caution is recommended in subjects with a history of pancreatitis (particularly in Ponatinib intolerant and failure population)</p> |
| Haemorrhage | <p>Subject should be monitored for signs or symptoms consistent with platelet dysfunction and coagulation derangement</p> | <p>Information included in the ICF for patient education</p> <p>Included in the schedule of assessments in the Protocol:</p> <p>Intensive haematology monitoring (inclusive of coagulation tests) included in Cycle 1 and 2 at weekly intervals and thereafter at every 3 monthly study visit</p> <p>Additional haematology tests and conduct of relevant specific evaluations will be at Investigator's discretion based on subject's clinical condition and standard medical practice, institutional and applicable protocol-specific guidelines</p> <p>Caution is indicated in subjects requiring medications that inhibit platelet function or anticoagulants</p> |
| Pregnancy | <p>The investigator is advised to make subjects aware of this risk</p> <p>To minimize the risk of teratogenic effects, K0706 should not be given to pregnant</p> | <p>Information included in the ICF for patient education</p> <p>Included in the Protocol:</p> <p>Detailed contraception requirement to be followed by study subject and his/her partner per protocol has been included in the Inclusion criteria</p> <p>Pregnant and Lactating women are not permitted per protocol inclusion/exclusion criteria</p> |

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| | <p>or lactating women</p> <p>In addition subjects intended to be treated with K0706 should be made aware of this risk and instructed to apply appropriate barrier contraceptive methods during treatment with K0706.</p> | <p>Women should be advised of the potential hazard to the foetus and to avoid becoming pregnant</p> <p>Pregnancy test is to be performed at 7 days prior to study entry and at appropriate study visits</p> <p>Guidance on steps to be undertaken in an inadvertent scenario of subject/pregnant partner included in the protocol</p> |
| Tumour lysis syndrome | <p>Subject should be monitored for signs or symptoms consistent with electrolyte imbalance, impaired renal outputs, particularly in Cycle 1 and 2 of the study</p> | <p>The investigator is advised to make subjects aware of this risk</p> <p>Included in the Protocol:</p> <p>Subject and Investigator have been given the option to provide in-house stay for Cycle 1 and 2 (Days 1, 2 and 3), additionally, provision has been made to extend subject's in-house stay based on investigator's assessment of subject's clinical condition</p> <p>Intensive haematology monitoring (inclusive of coagulation tests) included in Cycle 1 and 2 at weekly intervals and thereafter at every 3 monthly study visit</p> <p>Additional haematology tests and conduct of relevant specific evaluations will be at Investigator's discretion based on subject's clinical condition and standard medical practice, institutional and applicable protocol-specific guidelines</p> <p>Correction of clinically significant dehydration and treatment of high uric acid levels are recommended based on subject's clinical condition and standard medical practice, institutional and applicable protocol-specific guidelines</p> |
| Compromised wound healing and gastrointestinal perforation | <p>Subject should be monitored for signs or symptoms of delayed wound healing, pain abdomen, guarding and rigidity and signs</p> | <p>The investigator is advised to make subjects aware of this risk and Information included in the ICF for patient education</p> <p>Subject at risk of delayed wound healing or gastric perforation should be carefully evaluated as per the applicable protocol inclusion and exclusion criteria to check eligibility</p> <p>Included in the Protocol:</p> |

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| | of evolving shock and/or peritonitis | <p>Subject and Investigator have been given the option to provide in-house stay for Cycle 1 and 2 (Days 1, 2 and 3), additionally, provision has been made to extend Subject's in-house stay based on investigator's assessment of subject's clinical condition</p> <p>Monitoring in addition to intensive subject monitoring (inclusive of vitals, physical examination biochemistry, coagulation tests) included in Cycle 1 and 2 at weekly intervals and thereafter at every 3 monthly study visit must be provided in accordance to subject's clinical condition and investigator's judgement.</p> <p>Additional relevant specific evaluations and supportive treatment will be at Investigator's discretion based on subject's clinical condition and standard medical practice, institutional and applicable protocol-specific guidelines</p> |
|--|--------------------------------------|---|

13.3 APPENDIX III

The Appendix III which includes the details of Part A of the study will be provided on request.