Document Type:	Statistical Analysis Plan
Official Title:	An open label, non-randomized, Phase I dose escalation study to characterize safety, tolerability, pharmacokinetics and maximum tolerated dose of BAY 1163877 in subjects with refractory, locally advanced or metastatic solid tumors
NCT Number:	NCT01976741
Document Date:	11 Dec 2019

Title page

An open label, non-randomized, Phase I dose escalation study to characterize safety, tolerability, pharmacokinetics and maximum tolerated dose of BAY 1163877 in subjects with refractory, locally advanced or metastatic solid tumors

Phase I dose escalation pan-FGFR inhibitor (Rogaratinib)

Bayer study drug	BAY 1163877 / pan-FGFR inhibitor / rogaratinib		
Study purpose:	To determine the maximum tolerated dose (MTD)		
Clinical study phase:	I	**Date:**	11 DEC 2019
Study No.:	16443	**Version:**	2.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

Table of Contents

Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the curve
AUC(0-t_{last})	AUC from time 0 to the last data point > LLOQ after a single dose
AUC(0-t_{last})/D	AUC(0-t_{last}) divided by dose
%AUC(t_{last} - ∞)	Percentage of AUC from the last data point > LLOQ to infinity
AUC/D	AUC divided by dose
BC	Bladder cancer
b.i.d.	Twice daily
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
C_{max}	Maximum total drug concentration in plasma after a single dose
C_{max}/D	Maximum drug concentration in plasma after single dose Administration divided by dose
CR	Complete response
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events Version 4.03
CV	Coefficient of variation
d	Dose level
DOR	Duration of response
DOSD	Duration of stable disease
DOT	Duration of treatment
DLT	Dose-limiting toxicity
DSMT	Drug safety monitoring team
e.g.	Exempli gratia, for example
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
FGF	Fibroblast growth factors
FGFR	Fibroblast growth factor receptor
FU	Follow-up
GFR	Glomerular Filtration Rate
HR	Heart rate
IB	Investigator's Brochure
i.e.	*id est*, that is
KM	Kaplan-Meier
LAC	Lung adenocarcinoma
LLOQ	Lower limit of quantification
log	Logarithm
LS	Least squares
MAD	Median Absolute Difference
MCMC	Markov-Chain-Monte-Carlo
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NYHA	New York Heart Association (this abbreviation is usually used with roman digits to characterize the stage of heart failure, e.g. NYHA I)
p	Probability of observing a subject with DLTs during Cycle 1
PD	Pharmacodynamic(s)
PD	Progressive disease

p-ERK1/2	Phospho-extracellular signal-regulated kinase 1/2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
Qd	Probability of dose being the MTD
RECIST	Response Evaluation Criteria in Solid Tumors
RMAD	Relative Median Absolute Difference
ROW	Rest of the world
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SD	Standard deviation
sqNSCLC	Squamous non-small cell lung cancer
Td	(Tolerable) Probability that the DLT rate is <0.20, Pr(p <0.20|d), for a dose d
TEADR	Drug-related adverse event
TEAE	Treatment-emergent adverse event
t_{last}	Time to last observed concentration
t_{max}	Time to maximum observed concentration
TTP	Time to progression
vs	Versus, as opposed to
WHO DD	World Health Organization Drug Dictionary

1. Introduction

Fibroblast growth factors (FGF) and their corresponding receptor family (FGFR) drive crucial oncogenic signaling pathways including cell proliferation, survival and migration. FGFRs are commonly altered in various human tumor diseases, including FGFR1 amplification in squamous non-small cell lung cancer (sqNSCLC) or activating mutations of FGFR3 in bladder cancers. These changes contribute to tumor cell growth, sustained angiogenesis, invasion and metastasis and resistance against other therapies.

Rogaratinib (BAY 1163877) is an oral inhibitor of FGFR1, 2 and 3 and showed strong anti-tumor efficacy in pre-clinical models as a single agent as well as in combination with cytotoxic agents in FGFR pathway addicted tumor models.

The targeted application form is oral and preclinical data suggest low clearance and low volume of distribution resulting in a daily dose of 300 to 800 mg.

Further details can be found in the investigator's brochure (IB) (1), which contains comprehensive information on the study drug. The IB is available in the Trial Master File.

Additional information elaborating on the rationale of the study and the benefit-risk assessment can be found in the protocol.

This Statistical Analysis Plan (SAP) is based on the Clinical Study Protocol version 7.0 (including Amendment 7.0) (2).

2. Study Objectives

The primary objectives of this study are:

- To determine the safety and maximum tolerated dose (MTD) of BAY 1163877 in subjects with advanced solid organ malignancies

- To characterize the pharmacokinetics (PK) of BAY 1163877

The secondary objectives of this study are:

- To evaluate biomarker status, pharmacodynamic (PD) parameters, and tumor response.
- To assess the relative bioavailability of the tablet formulation in comparison to the solution formulation of BAY 1163877.

The exploratory objective of this study is:

- To evaluate selected immune parameters.

3. Study Design

This is a Phase I, first-in-human, open-label, non-randomized, multi-center, 3-part, dose escalation study of BAY 1163877 in sequential cohorts of subjects with refractory, locally advanced or metastatic solid tumors. The study will be conducted at multiple centers worldwide.

Study Part 1 will identify the MTD in subjects with any solid tumors (all comer) using an adaptive dose escalation design and expansion of cohort at MTD.

Study Part 2 will explore further the safety and PD of BAY 1163877 at the MTD identified in Part 1 in subjects with sqNSCLC, LAC, BC, and SCCHN to seek any evidence of preliminary clinical responses. Study Part 2 may start as soon as the MTD has been established in Part 1.

Study Part 3 will expand the safety database for patients on treatment with BAY1163877 at the MTD identified in Part 1 with sqNSCLC, LAC, and BC. In parallel, in Part 3 additional efficacy data will be collected and changes of selected immune parameters will be assessed.

The complete duration of the study (Part 1, Part 2, and Part 3) depends on the number of dose escalation steps in Part 1 and will be approximately 7 years.

Planned sample size:

Subjects will be enrolled in the pre-treatment phase of the study to recruit enough subjects with present high FGFR expression levels for the following study parts.

Targeted / planned enrollment:

- Study Part 1 / dose escalation (all comer): The total number of subjects will depend on the number of cohorts necessary to identify the MTD. Relative bioavailability of the tablet formulation in comparison to the solution formulation will be performed in all subjects enrolled in one of the dose escalation cohorts; pharmacokinetic data are needed in a minimum of 3 subjects for relative bioavailability assessment.
- Study Part 1 / MTD expansion (all comer): Additional subjects will be enrolled to have 20 evaluable “all comer” subjects treated at MTD.
- Study Part 2 / MTD expansion (*sqNSCLC* + *LAC* + *BC* + *SCCHN*): additional subjects will be enrolled to have 20 evaluable subjects with *sqNSCLC* or *LAC* and at least 30, up to maximum of 50 evaluable subjects with *BC* and at least 8 subjects with *SCCHN* treated at MTD.

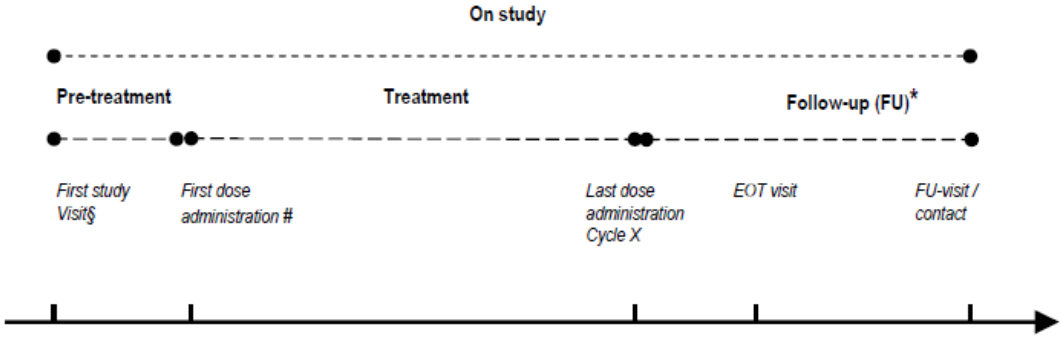
- Study Part 3 / MTD expansion "Safety cohort" (*sqNSCLC* + *LAC* + *BC*): additional subjects will be enrolled to have approximately 20 subjects with *sqNSCLC* or *LAC* and approximately 20, subjects with *BC* treated at MTD.

PK assessments will be performed in all subjects participating in study Part 1 / dose escalation and MTD expansion (all comer) and study Part 3/ MTD expansion "Safety cohort". Additionally, PK assessments are planned in at least 12 subjects participating in study Part 2 / MTD expansion (*sqNSCLC* + *LAC* + *BC* + *SCCHN*) such that valid PK data are available in 8 subjects and in approximately 8 subjects of the MTD expansion cohorts with impaired renal function at baseline. Food effect PK assessment is planned in approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2). Subjects participating in "food effect assessment" in study Part 2 may be included in the total sample size of 12 if all protocol requirements are met.

All subjects participating in either of the 3 MTD expansion cohorts (Part 1, Part 2, and Part 3 despite subjects with impaired renal function) will have 2 PK samples drawn for the purpose of exposure-response modelling on Day 1 of Cycles 2, 3, 4, and 5 (1 blood sample just before the morning dose of BAY 1163877 and 1 blood sample between 0.5 and 1.5 hours post-dose). Subjects in Part 3 will provide one PK sample within 1 hour of biopsy collection in Cycle 2. The dose needs to be taken under supervision and the time recorded.

Study periods:

Figure 3–1 Schematic presentation of the treatment design



§ The first study (screening) visit is scheduled within 7 days / within 28 days before administration of the first dose of BAY 1163877 (written informed consent for study treatment eligibility).
Subjects recruited for Part 1 or Part 2 MTD expansion cohorts have their first study visit before study (screening) visit to perform a biomarker analysis for subject stratification (mandatory written informed consent for FGFR expression / FGFR mutation testing). Those subjects who are eligible for participation in the MTD expansion cohort must additionally sign the informed consent for study treatment eligibility at the screening visit.

The first dose will be administered on Cycle 1, Day 1, except for subjects participating in relative bioavailability assessment ("tablet bridging cohort") and "food effect assessment" who will receive the first dose on Cycle 1, Day -3.

*Follow-up:
- EOT (End of Treatment) visit within 0-14 days of last dose of BAY 1163877
- FU (Follow-up) visit / contact at 30-35 days after last dose of BAY 1163877

In total, the "on study" period for all subjects comprises 3 phases (see Figure 3–1):

- Pre-treatment
    - Testing for FGFR and FGFR mutation (only for subjects recruited for Part 1, Part 2 or Part 3 MTD expansion cohorts)

- Screening

- Treatment
  - Study Part 1 / dose escalation + MTD expansion (all comer):

    Individual number of 21-day Cycles with BAY 1163877 monotherapy (tablet or solution) until disease progression or as along as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.
  - Study Part 1 / "tablet bridging cohort" (all comer):

    In one of the dose escalation cohorts, administration of a single dose of BAY 1163877 using the tablet formulation on Cycle 1, Day -3 followed by solution formulation starting Cycle 1 Day 1 as described above.
  - Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN):

    Individual number of 21-day Cycles with continuous BAY 1163877 monotherapy (tablet or solution) until disease progression or as along as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.
  - Study Part 1 (MTD expansion cohort) and Study Part 2 (sqNSCLC + LAC + BC + SCCHN) / "Food Effect Assessment":

    Approximately 8 subjects will receive single doses of BAY 1163877 on Cycle 1, Day -3 (after consumption of a high-fat, high-calorie breakfast) and on Cycle 1, Day 1 (after an overnight fast of at least 8 hours) followed by treatment according to the schedule described above starting on Cycle 1, Day 3.
  - Study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC):

    Individual number of 21-day Cycles with continuous BAY 1163877 monotherapy (tablet) until disease progression or as long as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.

Note: Treatment with BAY 1163877 at MTD in Part 1 (expansion cohort "all comer"), Part 2 (expansion cohort sqNSCLC + LAC + BC + SCCHN), and Part 3 (expansion cohort "Safety cohort", sqNSCLC + LAC + BC) can run in parallel.

- Follow-up (FU)
  - End of Treatment (EOT) visit 0-14 days after last dose of BAY 1163877
  - FU visit at 30-35 days after dose of BAY 1163877

The first screening visit is scheduled within 7 days / 28 days before administration of the first dose of BAY 1163877. The informed consent form will be signed by the subject before or at the first screening visit. The screening period ends just before start of treatment.

The treatment period starts on the day of the first administration of study treatment on Cycle 1, Day 1 or on Cycle 1, Day -3 ("tablet bridging cohort" and "food effect assessment") and ends with the last day when the study medication is administered in Cycle X. The length of treatment period may vary from subject to subject dependent on the number of individual treatment cycles. A Cycle for this study is defined as 21 days. There will be no break between cycles.

When a subject starts new anti-cancer therapy, he / she is no longer considered "on study".

An EOT visit will be performed for all subjects within 0-14 days after administration of the last dose of BAY 1163877. The FU visit for subjects who either discontinue prematurely or finish dosing with BAY 1163877 will be performed 30 - 35 days after the last study drug treatment. There will be no long-term (survival) FU period.

Treatment: Subjects with PK assessment (all subjects of study Part 1 and 3 and at least 12 subjects of study Part 2 and approximately 8 subjects of the MTD expansion cohorts with impaired renal function at baseline) will receive BAY 1163877 (tablet or solution) on a continuous schedule starting with single-dose administration on Cycle 1, Day 1, followed by a "drugfree day" (to enable single dose PK assessments except for subjects in Part 3 who will receive BAY 1163877 twice daily continuously with no "drug free day"). Treatment with BAY 1163877 will resume on Day 3 of Cycle 1 if no protocol-defined dose-limiting toxicities (DLTs) are reported. Starting on Cycle 1, Day 3, the study drug will be self-administered twice daily for the remaining 19 days of Cycle 1. For subsequent cycles, study drug will be administered twice daily for 21 days until disease progression or as long as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.

In one of the dose escalation cohorts in study Part 1 ("tablet bridging cohort"), relative bioavailability of the tablet formulation will be assessed by administration of a single dose of the tablet formulation on Cycle 1, Day -3. Starting with Cycle 1, Day 1, subjects enrolled in the "tablet bridging cohort" will continue with the solution formulation as described above. Depending on the results from the relative bioavailability assessment, subjects who initially start with solution formulation may be switched to tablet formulation in later cycles.

Approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2) will receive single doses of BAY 1163877 on Cycle 1, Day -3, after consumption of a high-fat, high-calorie breakfast and on Cycle 1, Day 1, after an overnight fast of at least 8 hours followed by treatment according to the schedule described above starting on Cycle 1, Day 3.

Subjects without PK assessment in study Part 2 will receive BAY 1163877 (tablet or solution) twice daily from Cycle 1, Day 1 ongoing.

At home, subjects will document the intake of study drug in a diary.

Subjects will continue receiving treatment until tumor progression, unacceptable toxicity, consent withdrawal, or subject withdrawal from the study at the discretion of the Investigator or his/her designated associate(s). As long as, in the judgment of the subject and the investigator, some benefit with evidence of tumor reduction or stable disease is being derived, dosing with BAY 1163877 may continue.

Determination of the MTD

An adaptive dose escalation design will be used to determine the MTD in study Part 1 / dose escalation (all comer). The MTD is defined as the highest dose that can be given such that not more than 20% of subjects experience a DLT during Cycle 1.

Without the occurrence of toxicities, dose escalation could be stopped and RP2D may be determined based on PK and/or PD results. The decision to continue treatment for an individual subjects will be made by the investigator according to the criteria specified in the protocol.

Each cohort will be evaluated after all subjects have completed the first 21 days of treatment (which will subsequently referred to as "Cycle 1") or early discontinued.

Safety monitoring will occur by telephone conferences with participation of the investigators and the sponsor on a regular basis.

At the time of dose escalation the available clinical safety information is discussed in a telephone conference by the involved investigators and representatives from the Sponsor including the Study Medical Expert as well as representatives of other clinical and if required further contributing functions (drug safety monitoring team – DSMT). During this telephone conference it will be judged if dose escalation can proceed as planned according to the procedure outlined below. Dose escalation for subsequent cohorts will only be considered after full evaluation of at least Cycle 1 safety data from the previous cohort.

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03) will be used to grade toxicities / adverse events.

The dose escalation will be performed as follows:

- Initially 3 subjects per dose level will be enrolled. In case 2 or more sites are conducting the dose escalation part, the initial enrolment of 4 subjects per dose level is optional.
- The starting dose of BAY 1163877 is 50 mg given as a single dose on Cycle 1, Day 1, and twice daily (b.i.d.) from Cycle 1, Day 3 (100 mg / day).
- The maximum dose escalation will be 2-fold.
- Possible daily doses of BAY 1163877 starting from 100 mg in increments of 100 mg.
- The possible maximum dose of BAY 1163877 is considered to be 550 mg b.i.d. (1100 mg / day). Higher doses might be explored after discussions between sponsor and investigators.
- If at least 1 subject out of 3 or 1 out of 4 in a cohort has DLTs or if at least 2 subjects report drug-related AEs (CTCAE v4.03) of Grade $\geqslant$ 2, any further dose escalation, de-escalation or cohort expansion will be decided in consultation between all investigator(s), and the sponsor (within the DSMT) after consideration of all available safety data of the previous cohorts. Any subsequent dose will be selected in order to determine the MTD.

  Model-based dose-response analysis of the DLT rates will be performed during these interim reviews in order to guide the dose decision. The model-based dose selection procedure is considering data at all dose levels (not just at the last cohort). The dose predicted to yield 20% DLT rates will be reported from that model as a best candidate for the next cohort.

  The final decision about the next dose will be made by the sponsor in consultation with all investigators (DSMT).

  If the selected dose is larger than the last dose tested, then escalation will be pursued. If it is lower, a de-escalation step will occur.

  Cohort expansion will occur when a previously tested dose is selected again for the next cohort of 3 subjects.

  Expansions at any given dose up to a total of 9 subjects are allowed. In principle, the selection of a next dose level where the predicted DLT rate is close to 20% should insure that the next dose tested will remain safe.

Nevertheless, the following constraint will be added in order to protect subject safety during the adaptive dose selection decisions:

- If 2 out of 3 (or 2 out of 4), at least 4 out of 6 (or at least 5 out of 9) subjects experience DLTs at a given dose level, only lower doses will be given in all subsequent cohorts because the probability that the dose is above the MTD is very large (above 95.4%).
- The dose-escalation procedure will be stopped as soon as:
  - the MTD has been defined with good precision (i.e. the coefficient of variation for the MTD is lower than or close to 40%)

    or
  - at any time when the selected dose level for the next cohort has already been given in 9 subjects.

If the dose escalation stops, the sample size for the MTD cohort will be expanded up to a total of 20 evaluable subjects (study Part 1 / MTD expansion cohort (all comer)).

No intra-subject dose escalation is permitted. Dose interruptions and / or dose reductions may be required based on individual safety and tolerability.

Variables are specified in the Clinical Study Protocol (2).

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA), R release 2.4.1 or higher and BRugs release 0.3-3 or higher. All variables will be analyzed by descriptive statistical methods. The number of data available, mean, standard deviation, minimum, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

Data displays will follow the standard table catalogs for oncology standards, global standards, and clinical pharmacology standards, respectively.

The pharmacokinetic parameters will be evaluated statistically in accordance with pertinent company guidelines.

The following treatment groups will be analyzed:

- Total Dose Escalation – It contains all cohorts from the escalation phase:
  - 100 mg BAY 1163877 (50 mg solution BID)
  - 200 mg BAY 1163877 (100 mg solution BID)
  - 400 mg BAY 1163877 (200 mg tablet BID)
  - 800 mg BAY 1163877 (400 mg tablet BID)
  - 1200 mg BAY 1163877 (600 mg tablet BID)
  - 1600 mg BAY 1163877 (800 mg tablet BID)
- Expansion All Comers – Expansion phase, 1600 mg BAY 1163877 (800 mg tablet BID), cancer type does not fit the categories below
- Expansion Bladder – Expansion phase, 1600 mg BAY 1163877 (800 mg tablet BID), cancer type: bladder cancer

- Expansion Head & Neck – Expansion phase, 1600 mg BAY 1163877 (800 mg tablet BID), cancer type: squamous carcinoma cell head and neck
- Expansion NSCLC – Expansion Phase, 1600 mg BAY 1163877 (800 mg tablet BID), cancer type: lung adenocarcinoma / squamous cell carcinoma

The categories of region used for subgroup analysis will be derived for each subject by using the variable country (location of the respective site).

4.2 Handling of Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been administered at least 1 dose of the study drug (BAY 1163877).

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see above) is regarded a "screening failure".

Subjects who discontinue due to a DLT will NOT be replaced.

Subjects who discontinue during the first cycle of therapy (Cycle 1) due to any reason other than a DLT and / or related toxicity, and subjects who took less than 80% of the required study drug (BAY 1163877) in Cycle 1 will be replaced to ensure 3 evaluable subjects per cohort for the determination of MTD and PK of BAY 1163877. Subjects who discontinue after the first cycle (Cycle 1) will not be replaced.

Subjects enrolled in Study Part 1 / MTD expansion (all comer) with insufficient paired biopsy samples will be replaced to ensure at least 10 subjects with paired biopsy samples for p-ERK1/2 analysis.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form (CRF).

Missing data will not be replaced. Possible impact of missing values on the analysis will be discussed in the clinical study report.

4.4 Interim Analyses and Data Monitoring

Safety data will be reviewed on an ongoing basis during study Part 1 / dose escalation (all comer). Bayesian dose-response and / or PK / PD modeling of DLTs rates and CTCAE v4.03 gradings may be performed after selected cohorts in order to generate additional relevant information for the adaptive dose selection decisions. The sponsor together with all investigators will review all available data and make the final decision as to dose escalation, de-escalation or cohort expansion during the adaptive dose escalation part. This group will also determine when to implement predefined stopping rules.

No interim analysis is planned during dose expansion at MTD in study Part 1 (MTD expansion cohort "all comer"), study Part 2 (MTD expansion cohort "sqNSCLC + LAC+ BC + SCCHN") or study Part 3 (MTD expansion cohort "Safety cohort").

4.5 Data Rules

4.5.1 Baseline

Unless otherwise stated, baseline is defined as the last pre-dose assessment before first study drug administration or as the last pre-dose assessment before the time period being analyzed.

4.5.2 Unscheduled Measurements

If control measurements for a planned timepoint before study drug administration are available, the last value (i.e. of the measurement closest to the study drug administration) will be used for the calculation of descriptive statistics. If control measurements for a planned timepoint after study drug administration are available, the planned measurement will be used for the calculation of descriptive statistics.

Further applicable data rules are described in section 6 “Statistical Methodology”.

4.6 Blind Review/Validity Review

The results of the validity review meeting will be documented in the Validity Review Report and may comprise decisions and details relevant for statistical evaluation. Any changes to the statistical analysis prompted by the results of the validity review meeting will be documented in an amendment and, if applicable, in a supplement to this SAP or will be documented in the clinical study report.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s) (see section 4.6).

Safety analysis set

All subjects who received at least 1 dose of BAY 1163877 will be included in the safety evaluation.

MTD analysis set

All subjects who completed Cycle 1 or discontinued during Cycle 1 due to an adverse event or DLT in the dose escalation part will be included in the MTD evaluation.

Efficacy analysis set

All subjects who received at least 1 dose of BAY 1163877 and who have post-baseline efficacy data available will be included in the efficacy evaluations.

Pharmacodynamic analysis set

All subjects with evaluable PD data and who complete the study without major changes versus protocol will be included in the evaluation of PD.

Pharmacokinetic analysis set

All subjects with valid pharmacokinetic data will be included in the evaluation of pharmacokinetic concentrations and parameters.

6. Statistical Methodology

The treatment groups to be analyzed are defined in section 4.1.

6.1 Population characteristics

Analyses for population characteristics will be performed for the safety population on the treatment groups if not stated otherwise. If the pharmacokinetic population, pharmacodynmic population, MTD population or efficacy population differ from the safety population, summary statistics and frequency tables for the respective population will be provided as well. The results will be displayed by region (Asia, ROW, and total), if reasonable.

6.1.1 Disposition

Disposition at the end of screening will be summarized for subjects who signed the informed consent for FGFR testing and for all subjects who signed the main informed consent, respectively. All enrolled subjects population comprises subjects who signed any informed consent. Disposition at the end of Treatment and for the Safety follow-up will be summarized by treatment groups for all subjects assigned to treatment.

6.1.2 Protocol deviations

Frequency tables of protocol deviations by category and deviation coded term will be summarized by treatment group.

6.1.3 Demographics and other baseline characteristics

Demographics and general baseline characteristics will be summarized by treatment group. Quantitative data will be summarized by arithmetic mean, SD, median, minimum and maximum. Frequency tables will be provided for qualitative data. Variables include sex, race, ethnicity, age (as reported on the eCRF), weight, height, body mass index (BMI), and NYHA functional class.

Baseline cancer characteristics will be summarized by treatment group. Variables include for example baseline ECOG Performance Status, number of target lesions, number of non-target lesions, cancer type, histology, status of primary tumor, stage at initial diagnosis, grading at initial diagnosis, clinical status at study entry, stage at study entry, time since initial diagnosis. Please note that the list of the above mentioned parameters is not extensive.

In addition, demographics and baseline cancer characteristics will be summarized for all subjects who signed the informed consent for FGFR testing.

6.1.4 Prior and Concurrent Medication/Therapy

Prior anti-cancer therapy and surgical therapeutic procedures will be summarized by treatment group. The counts and percentages of patients who were previously treated using radiotherapy, local anti-cancer therapy, systemic anti-cancer therapy, and who had any diagnostic and therapeutic procedure(s) will be presented. The number of patients with radiotherapy and systemic or local anti-cancer therapy will be presented by intent of procedure and number of regimens/procedures. In addition, concurrent radiotherapy, diagnostic and therapeutic procedures will be summarized. Prior and concomitant medications will be coded to generic terms using the World Health Organization Drug Dictionary (WHO

DD) Version 2017SEP or later and summarized by treatment group. The version used in analyses will be presented in the clinical study report.

6.1.5 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later. The version used in analyses will be presented in the clinical study report. Medical history data will be summarized by system organ class, high level term, and preferred term by treatment group.

6.2 Efficacy

Efficacy analyses will be performed on the efficacy analysis set.

Tumor response

Efficacy data, such as best tumor response, will be summarized using descriptive statistics and will be graphically displayed if appropriate. The correlation between PD parameters and selected safety, efficacy, or PK parameters may be graphically displayed. Further statistical analyses may be conducted.

The efficacy analysis will include descriptive analyses on response rate, progression-free survival (PFS), time to progression (TTP), duration of response (DOR), and duration of treatment (DOT).

Response as defined by RECIST v.1.1: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). Response and progression will be evaluated in this trial using the new international criteria proposed by the RECIST committee for solid tumor.

PFS is defined as the time (days) from the date of the first dose of study drug to the date of the first observed disease progression (radiological or clinical) or death due to any cause, if death occurs before progression is documented. PFS for subjects without tumor progression at the time of analysis will be censored at their last date of tumor evaluation.

TTP is defined as the time from start of study treatment until first observed disease progression (radiological or clinical). In comparison to PFS, TTP does not consider death as an event.

DOR (for partial and complete response (PR/CR)) is defined as the time (days) from the first documented objective response of PR or CR, whichever is noted earlier, to disease progression or death (if death occurs before progression is documented).

Kaplan-Meier (KM) product-limit estimates for median, 25th and 75th percentile with its 95% CI together with total number of subjects, total censored and total events will be provided for PFS and TTP per treatment. In addition KM survival curves will be presented for each treatment group.

Best overall tumor response according to RECIST criteria will be summarized by treatment group and region (Asia, ROW, and total) using frequency counts.

Best % Change in Target Lesion sum of diameter from Baseline will be displayed graphically for all subjects from worst to best in a waterfall plot.

Subgroup analysis will be performed by prior immunotherapy information (prior immunotherapy vs. no prior immunotherapy) .

6.3 Pharmacokinetics/pharmacodynamics

6.3.1 Pharmacokinetics

Analyses will be performed on the Pharmacokinetic analysis set. A pooled treatment group (all 800mg BID patients, regardless of study part or tumor type) will be included for PK analyses.

The concentration-times courses of all analytes will be tabulated for each cohort by treatment group. The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation, and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms), minimum, median, maximum value, and the number of measurements. Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value, a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Individual and geometric mean concentration vs. time curves of all analytes (using the actual sampling times for individual plots and the planned sampling times for mean plots) will be plotted by cohort using both linear and semilogarithmic scale.

The amount and percent of drug excreted into urine will be graphically illustrated for the sampling interval as well as for the whole sampling period (bar-charts for the individual data and the arithmetic mean including standard deviation).

Pharmacokinetic characteristics ($t_{max,}$ $t_{last,}$ and %AUC(t_{last} - ∞) excluded) will be summarized by the statistics mentioned above. t_{max} and t_{last} will be described utilizing minimum, maximum, and median as well as frequency counts.

PK Dose proportionality

To investigate dose proportionality, an explorative ANOVA, including the factor cohort, will be performed on the log-transformed values of C_{max}/D, AUC(0-t_{last})/D, and AUC/D calculated from single (where applicable) and multiple dose PK profiles.

Bridging: tablet vs solution relative bioavailability

PK parameters of different dose levels will be analyzed together for the assessment of relative bioavailability.

In order to evaluate the relative bioavailability of the tablet formulation, tablet C_{max}/D, AUC(0-t_{last})/D, and AUC/D on Cycle 1, Day -3 will be compared to solution C_{max}/D, AUC(0-t_{last})/D, AUC/D on Cycle 1, Day 1 for all analytes. If needed, additional PK parameters may be used for relative bioavailability assessment. The logarithms of these PK parameters will be analyzed using analysis of variance (ANOVA) including subject and formulation effects.

Based on these analyses, point estimates (LS-means) and exploratory 90% confidence intervals for the ratios (tablet/solution) of C_{max}/D, AUC(0- t_{last})/D, and AUC/D will be calculated by re-transformation of the logarithmic data using the intra-individual standard deviation of the ANOVA.

Subjects to be included in the relative bioavailability evaluation (“tablet bridging cohort”) should have evaluable pharmacokinetic data on both Cycle 1, Day -3 and Cycle 1, Day 1.

Food effect

In order to evaluate the effect of food on BAY 1163877, C_{max} and AUC(0-t_{last}) on Cycle 1, Day -3 and C_{max} and AUC(0-t_{last}) on Cycle 1, Day 1 will be compared. The logarithms of C_{max} and AUC(0-t_{last}) will be analyzed using ANOVA including subject and food effect.

Based on these analyses, point estimates (LS-means) and exploratory 90% confidence intervals for the ratios (high-fat, high-calorie meal / fasting) of C_{max} and AUC(0- t_{last}) will be calculated by re-transformation of the logarithmic data using the intra-individual standard deviation of the ANOVA.

The PK paramteres C_{max}/D, AUC(0-t_{last})/D, AUC/D, C_{max}. and AUC(0-t_{last}) will be graphically illustrated using stickplots. Scatterplots of the PK parameters C_{max}/D, AUC(0-t_{last})/D, AUC/D will be created.

6.3.2 Pharmacodynamic data

Cardiovascular parameters will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented by cohort for the original data as well as for the difference to baseline (defined as the pre-dose assessment of the day being analyzed), if applicable.

Graphical displays of individual data as well as mean values with standard deviation may be included for absolute values as well as change from baseline.

6.4 Safety

The analyses will be performed on the safety analysis set and results will be displayed by region (Asia, ROW, and total), if reasonable.

6.4.1 Study drug exposure

Duration of treatment will be summarized using summary statistics. Actual dose, total amount of dose, and percent of planned dose during study period will be also summarized. Dose modification with reason will be summarized.

6.4.2 Maximum tolerated dose

Individual listings of DLTs with CTCAE v4.03 code and grade will be presented.

The incidence of subjects with DLTs during Cycle 1 will be summarized by treatment and, if possible, modeled as a function of BAY 1163877 dose using Bayesian logistic regression. The moderately-informative independent priors used during the interim dose response analysis (see Section 6.5 for details) as well as non-informative priors will be used for this analysis to assess sensitivity of the estimates. Parameter estimates and model predictions will be reported with 90% credibility sets. The MTD will be computed as a derived function of model parameters as:

$$\text{MTD} = (\log(0.2/0.8)\text{-intercept})/\text{slope}.$$

The posterior distribution of the MTD will be summarized in tabular and graphical formats.

6.4.3 Adverse Events

Adverse events will be analyzed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) version 4.03. In addition a separate set of AE tables will be generated using MedDRA terms.

The incidence of treatment-emergent adverse events (TEAEs), drug-related adverse events (TEADRs), treatment-emergent and drug-related serious adverse events (SAEs), respectively, will be summarized by treatment group CTCAE body system code and worst NCI-CTCAE grade. TEAEs, SAEs, drug-related TEAEs, and drug-related SAEs for events of Grade 3/4/5 will be summarized similarly.

AEs are considered treatment emergent if they have started or worsened after the first study drug administration up to 30 days after the end of treatment with study drug.

Frequency tables will also be provided for the changes of CTCAE grade from pre-treatment and changes of worst CTCAE grade under treatment.

In addition, TEAEs, SAEs, drug-related TEAEs, and drug-related SAEs will be summarized by MedDRA (Version 20.1 or later) system organ class, preferred term and worst NCI-CTCAE grade. The same will be also summarized similarly for events of Grade 3/4/5.

Patient listings of all AEs, SAEs, AEs leading to dose reduction, AEs leading to dose interruption, AEs leading to discontinuation, dose limiting toxicity AEs, and deaths will be presented.

6.4.4 Safety Parameters

Quantitative data (vital signs, ECG, ECOG performance status) will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum, and maximum. These summary statistics will be presented by treatment group for the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data. Graphical displays of mean values with standard deviation will be provided.

The average of triplicate quantitative ECG parameters at all ECG time points will be used for all analyses.

Laboratory data outside the reference range will be listed and flagged with ‘L’ for low and ‘H’ for high. The incidence of laboratory data outside the reference range (low, high) will be summarized by treatment groupin frequency tables.

Calcium, phosphate and the product of calcium and phosphate will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented by cohort for the original data as well as for the difference to baseline (defined as the pre-dose assessment of the day being analyzed).

Graphical displays of mean values with standard deviation will be included for absolute values as well as change from baseline.The number of subjects with at least one phosphate level > 5.5 mg/dL, with at least one phosphate level > 7 mg/dL and with at least one phosphate level > 9 mg/dL will be summarized using frequency tables.

The number of subjects with at least one value > 70 mg^2/dL^2 of the product phosphate and calcium will be summarized using frequency tables.

The incidence of laboratory toxicities will also be summarized by worst CTCAE v4.03 grade and by treatment group. Frequency tables will also be provided for the changes of worst CTCAE v4.03 grade after start of treatment versus baseline.

6.5 Interim dose response modeling

MTD determination takes place at the end of the dose escalation phase and is based on the DLT rate during Cycle 1.

The following Bayesian dose-response analysis of the DLT rates will be performed during the interim reviews in order to guide the dose escalation decision.

Bayesian logistic regression

The analysis is based on a method reported by Tibaldi et al (3).

A range of doses will be tested, including possibly 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 and 1100 mg. Additional or alternative dose levels may be chosen. These possible dose levels are labeled as $d = 1, \ldots, N$, where N is the maximum number of dose levels for the study. The probability, p, of observing a subject with DLTs during Cycle 1 is modeled as a function of dose:

$$\log\left(\frac{p}{1-p}\right) = \text{intercept} + \text{slope} * d$$

In this trial, the MTD is defined as the predicted dose where the DLT probability is 20%:

$$\text{MTD} = (\log(0.2/0.8)\text{-intercept})/\text{slope}.$$

A Bayesian analysis will be performed, considering the following independent priors for the model parameters:

- intercept has a normal distribution with mean equal to -3 and variance equal to 1.
- slope has a positive normal distribution with mean equal to 0.0015 and variance equal to 0.003.

These priors were specified in the protocol. They are moderately-informative and were considered plausible in the context of the current dose escalation scheme and indication.

The posterior distribution of model parameters and the MTD will be estimated with the R package BRugs using MCMC techniques and considering at least 10000 simulations after convergence of the Markov chain.

The precision of the MTD will be monitored by calculating the relative median absolute difference (RMAD% = 100*mad/median). This robust estimator is a suitable statistic to quantify variability in asymmetric distributions. A low RMAD(MTD)% value indicates good precision.

In addition, the following posterior probabilities will be calculated for each dose level in the candidate set:

- Td = (tolerable) Probability that the DLT rate is below 0.20, Pr(p <0.20| d), for a dose d.
- Qd = Probability of dose d being the MTD. This is the probability that d is the maximum dose from the candidate set where p<20%.

Guidance for selection of next dose

The posterior density of the MTD and the Qd probabilities in the candidate set are the two main instruments that will be reported to guide dose selection. They indicate on a continuous

and discrete scale respectively the desirability for a dose to become the next choice. The larger the value, the more likely the corresponding dose is the MTD.

We recommended to compare the desirability of various dose candidates prior to making the dose selection decision. Doses with a high desirability are more likely to be the MTD, so they are preferred. When several doses have a similarly high desirability value, they are equally likely to become the MTD and the choice may be driven by other factors.

To avoid over dosing, only doses at most 2-fold larger than the maximum dose tested can be considered as candidates for the escalation process.

Guidance for stopping the dose escalation

Four indicators will be monitored and the dose escalation process may be terminated as soon as either statistic has reached a target threshold, as defined in the protocol.

1. MTD precisely estimated: CV(MTD) calculated as the inter-quartile range over the median is lower than 40%.
2. Maximum possible dose is safe T_N >80%.
3. Minimum dose tested (100 mg) is toxic (T_1 <20%).
4. Total sample size for next dose is already equal to 9.

Criteria 1. to 3. will end up in a conclusive dose escalation study. The conclusion will be either that 1. the MTD has been found , 2. all doses are safe or 3. they are all toxic. Criterion 4. does not lead to any interpretation about DLTs but it is a practical constraint to limit the overall duration of the study.

7. Document history and changes in the planned statistical analysis

- Approval of SAP, Version 1.0, 22 Mar 2018
- Approval of SAP Supplement, 11 Dec 2019
  - Added clarification regarding determination of MTD during the dose escalation part (section 3, section 51, section 6.5)
  - Update of treatment groups as specified in the TLF Specifications (section 4.2)
  - Deleted the statement on separate TLFs by study part (section 6)
  - Added population characteristics summaries for additional populations (section 6.1)
  - Added definition of all enrolled subjects (section 6.1.1)
  - Deleted overall survival and duration of stable disease as they are not efficacy endpoints in the protocol (section 6.2)
  - Added a pooled treatment group and deleted a repetition in the PK section (section 6.3)
  - Wording was harmonized throughout the document (treatment groups instead of arms/cohorts)

8. References

(1) Investigator's Brochure BAY 1163877 (Rogaratinib), Version 8.0, dated 10 Oct 2017.

(2) Integrated Clinical Study Protocol No. 1163877 / 16443, Version 7.0, dated 16 Mar 2017.

(3) Tibaldi FS, Beck BH, A. B. Implementation of a Phase 1 adaptive clinical trial in a treatment of type 2 diabetes. Drug Inf J. 2008;42(5):455-65.

An open label, non-randomized, Phase I dose escalation study to characterize safety, tolerability, pharmacokinetics and maximum tolerated dose of BAY 1163877 in subjects with refractory, locally advanced or metastatic solid tumors

Phase I dose escalation pan-FGFR inhibitor (Rogaratinib)

Bayer study drug	BAY 1163877 / pan-FGFR inhibitor / rogaratinib		
Study purpose:	To determine the maximum tolerated dose (MTD)		
Clinical study phase:	I	**Date:**	22 Mar 2018
Study No.:	16443	**Version:**	1.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

Table of Contents

Abbreviations

AE	adverse event
ANOVA	analysis of variance
AUC	Area under the curve
AUC(0-t_{last})	AUC from time 0 to the last data point > LLOQ after a single dose
AUC(0-t_{last})/D	AUC(0-t_{last}) divided by dose
%AUC(t_{last} - ∞)	percentage of AUC from the last data point > LLOQ to infinity
AUC/D	AUC divided by dose
BC	bladder cancer
b.i.d.	twice daily
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
C_{max}	maximum total drug concentration in plasma after a single dose
C_{max}/D	maximum drug concentration in plasma after single dose administration divided by dose
CR	Complete response
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events Version 4.03
CV	coefficient of variation
d	Dose level
DOR	Duration of response
DOSD	Duration of stable disease
DOT	Duration of treatment
DLT	dose-limiting toxicity
DSMT	Drug safety monitoring team
e.g.	exempli gratia, for example
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of treatment
FGF	Fibroblast growth factors
FGFR	fibroblast growth factor receptor
FU	Follow-up
GFR	Glomerular Filtration Rate
HR	Heart rate
IB	Investigator's Brochure
i.e.	*id est*, that is
KM	Kaplan-Meier
LAC	lung adenocarcinoma
LLOQ	lower limit of quantification
log	logarithm
LS	Least squares
MAD	Median Absolute Difference
MCMC	Markov-Chain-Monte-Carlo
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NYHA	New York Heart Association (this abbreviation is usually used with roman digits to

	characterize the stage of heart failure, e.g. NYHA I)
OS	overall survival
p	probability of observing a subject with DLTs during Cycle 1
PD	Pharmacodynamic(s)
PD	Progressive disease
p-ERK1/2	phospho-extracellular signal-regulated kinase 1/2
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	Partial response
Qd	probability of dose d being the MTD
RECIST	Response Evaluation Criteria in Solid Tumors
RMAD	Relative Median Absolute Difference
ROW	Rest of the world
RP2D	recommended Phase II dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SD	standard deviation
sqNSCLC	squamous non-small cell lung cancer
Td	(tolerable) probability that the DLT rate is <0.20, Pr(p <0.20|d), for a dose d
TEADR	drug-related adverse event
TEAE	treatment-emergent adverse event
t_{last}	Time to last observed concentration
t_{max}	Time to maximum observed concentration
TTP	time to progression
vs	versus, as opposed to
WHO DD	World Health Organization Drug Dictionary

1. Introduction

Fibroblast growth factors (FGF) and their corresponding receptor family (FGFR) drive crucial oncogenic signaling pathways including cell proliferation, survival and migration. FGFRs are commonly altered in various human tumor diseases, including FGFR1 amplification in squamous non-small cell lung cancer (sqNSCLC) or activating mutations of FGFR3 in bladder cancers. These changes contribute to tumor cell growth, sustained angiogenesis, invasion and metastasis and resistance against other therapies.

Rogaratinib (BAY 1163877) is an oral inhibitor of FGFR1, 2 and 3 and showed strong anti-tumor efficacy in pre-clinical models as a single agent as well as in combination with cytotoxic agents in FGFR pathway addicted tumor models.

The targeted application form is oral and preclinical data suggest low clearance and low volume of distribution resulting in a daily dose of 300 to 800 mg.

Further details can be found in the investigator's brochure (IB)[1], which contains comprehensive information on the study drug. The IB is available in the Trial Master File.

Additional information elaborating on the rationale of the study and the benefit-risk assessment can be found in the protocol.

This Statistical Analysis Plan (SAP) is based on the Clinical Study Protocol version 7.0 (including Amendment 7.0)[2].

2. Study Objectives

The primary objectives of this study are:

- To determine the safety and maximum tolerated dose (MTD) of BAY 1163877 in subjects with advanced solid organ malignancies
- To characterize the pharmacokinetics (PK) of BAY 1163877

The secondary objectives of this study are:

- To evaluate biomarker status, pharmacodynamic (PD) parameters, and tumor response.
- To assess the relative bioavailability of the tablet formulation in comparison to the solution formulation of BAY 1163877.

The exploratory objective of this study is:

- To evaluate selected immune parameters.

3. Study Design

This is a Phase I, first-in-human, open-label, non-randomized, multi-center, 3-part, dose escalation study of BAY 1163877 in sequential cohorts of subjects with refractory, locally advanced or metastatic solid tumors. The study will be conducted at multiple centers worldwide.

Study Part 1 will identify the MTD in subjects with any solid tumors (all comer) using an adaptive dose escalation design and expansion of cohort at MTD.

Study Part 2 will explore further the safety and PD of BAY 1163877 at the MTD identified in Part 1 in subjects with sqNSCLC, LAC, BC, and SCCHN to seek any evidence of preliminary clinical responses. Study Part 2 may start as soon as the MTD has been established in Part 1.

Study Part 3 will expand the safety database for patients on treatment with BAY1163877 at the MTD identified in Part 1 with sqNSCLC, LAC, and BC. In parallel, in Part 3 additional efficacy data will be collected and changes of selected immune parameters will be assessed.

The complete duration of the study (Part 1, Part 2, and Part 3) depends on the number of dose escalation steps in Part 1 and will be approximately 7 years.

Planned sample size:

Subjects will be enrolled in the pre-treatment phase of the study to recruit enough subjects with present high FGFR expression levels for the following study parts.

Targeted / planned enrollment:

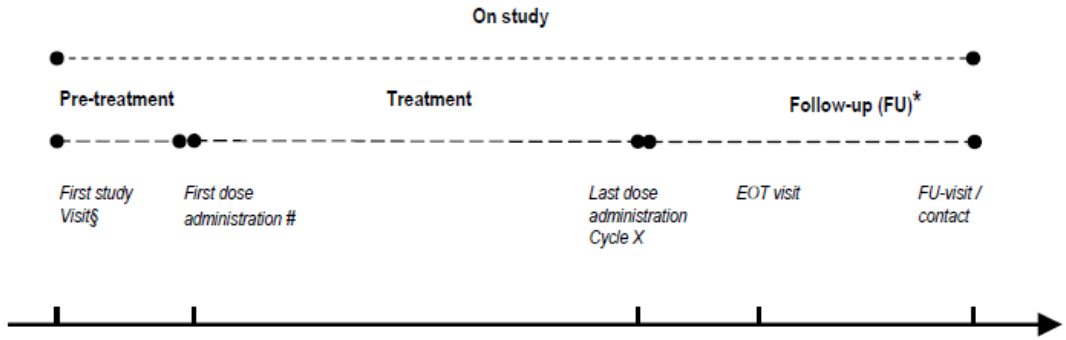
- Study Part 1 / dose escalation (all comer): The total number of subjects will depend on the number of cohorts necessary to identify the MTD. Relative bioavailability of the tablet formulation in comparison to the solution formulation will be performed in all subjects enrolled in one of the dose escalation cohorts; pharmacokinetic data are needed in a minimum of 3 subjects for relative bioavailability assessment.
- Study Part 1 / MTD expansion (all comer): Additional subjects will be enrolled to have 20 evaluable “all comer” subjects treated at MTD.
- Study Part 2 / MTD expansion (*sqNSCLC* + *LAC* + *BC* + *SCCHN*): additional subjects will be enrolled to have 20 evaluable subjects with *sqNSCLC* or *LAC* and at least 30, up to maximum of 50 evaluable subjects with *BC* and at least 8 subjects with *SCCHN* treated at MTD.
- Study Part 3 / MTD expansion “Safety cohort” (*sqNSCLC* + *LAC* + *BC*): additional subjects will be enrolled to have approximately 20 subjects with *sqNSCLC* or *LAC* and approximately 20, subjects with *BC* treated at MTD.

PK assessments will be performed in all subjects participating in study Part 1 / dose escalation and MTD expansion (all comer) and study Part 3/ MTD expansion “Safety cohort”. Additionally, PK assessments are planned in at least 12 subjects participating in study Part 2 / MTD expansion (*sqNSCLC* + *LAC* + *BC* + *SCCHN*) such that valid PK data are available in 8 subjects and in approximately 8 subjects of the MTD expansion cohorts with impaired renal function at baseline. Food effect PK assessment is planned in approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2). Subjects participating in “food effect assessment” in study Part 2 may be included in the total sample size of 12 if all protocol requirements are met.

All subjects participating in either of the 3 MTD expansion cohorts (Part 1, Part 2, and Part 3 despite subjects with impaired renal function) will have 2 PK samples drawn for the purpose of exposure-response modelling on Day 1 of Cycles 2, 3, 4, and 5 (1 blood sample just before the morning dose of BAY 1163877 and 1 blood sample between 0.5 and 1.5 hours post-dose). Subjects in Part 3 will provide one PK sample within 1 hour of biopsy collection in Cycle 2. The dose needs to be taken under supervision and the time recorded.

Study periods:

Figure 3—1 Schematic presentation of the treatment design



§ The first study (screening) visit is scheduled within 7 days / within 28 days before administration of the first dose of BAY 1163877 (written informed consent for study treatment eligibility).
Subjects recruited for Part 1 or Part 2 MTD expansion cohorts have their first study visit before study (screening) visit to perform a biomarker analysis for subject stratification (mandatory written informed consent for FGFR expression / FGFR mutation testing). Those subjects who are eligible for participation in the MTD expansion cohort must additionally sign the informed consent for study treatment eligibility at the screening visit.

The first dose will be administered on Cycle 1, Day 1, except for subjects participating in relative bioavailability assessment ("tablet bridging cohort") and "food effect assessment" who will receive the first dose on Cycle 1, Day -3.

*Follow-up:
- EOT (End of Treatment) visit within 0-14 days of last dose of BAY 1163877
- FU (Follow-up) visit / contact at 30-35 days after last dose of BAY 1163877

In total, the "on study" period for all subjects comprises 3 phases (see Figure 3—1):

- Pre-treatment
    - Testing for FGFR and FGFR mutation (only for subjects recruited for Part 1, Part 2 or Part 3 MTD expansion cohorts)
    - Screening
- Treatment
    - Study Part 1 / dose escalation + MTD expansion (all comer):

      Individual number of 21-day Cycles with BAY 1163877 monotherapy (tablet or solution) until disease progression or as along as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.
    - Study Part 1 / "tablet bridging cohort" (all comer):

      In one of the dose escalation cohorts, administration of a single dose of BAY 1163877 using the tablet formulation on Cycle 1, Day -3 followed by solution formulation starting Cycle 1 Day 1 as described above.
    - Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN):

Individual number of 21-day Cycles with continuous BAY 1163877 monotherapy (tablet or solution) until disease progression or as along as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.

- Study Part 1 (MTD expansion cohort) and Study Part 2 (sqNSCLC + LAC + BC + SCCHN) / "Food Effect Assessment":

  Approximately 8 subjects will receive single doses of BAY 1163877 on Cycle 1, Day -3 (after consumption of a high-fat, high-calorie breakfast) and on Cycle 1, Day 1 (after an overnight fast of at least 8 hours) followed by treatment according to the schedule described above starting on Cycle 1, Day 3.

- Study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC):

  Individual number of 21-day Cycles with continuous BAY 1163877 monotherapy (tablet) until disease progression or as long as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.

Note: Treatment with BAY 1163877 at MTD in Part 1 (expansion cohort "all comer"), Part 2 (expansion cohort sqNSCLC + LAC + BC + SCCHN), and Part 3 (expansion cohort

"Safety cohort", sqNSCLC + LAC + BC) can run in parallel.

- Follow-up (FU)
  - End of Treatment (EOT) visit 0-14 days after last dose of BAY 1163877
  - FU visit at 30-35 days after dose of BAY 1163877

The first screening visit is scheduled within 7 days / 28 days before administration of the first dose of BAY 1163877. The informed consent form will be signed by the subject before or at the first screening visit. The screening period ends just before start of treatment.

The treatment period starts on the day of the first administration of study treatment on Cycle 1, Day 1 or on Cycle 1, Day -3 ("tablet bridging cohort" and "food effect assessment") and ends with the last day when the study medication is administered in Cycle X. The length of treatment period may vary from subject to subject dependent on the number of individual treatment cycles. A Cycle for this study is defined as 21 days. There will be no break between cycles.

When a subject starts new anti-cancer therapy, he / she is no longer considered "on study".

An EOT visit will be performed for all subjects within 0-14 days after administration of the last dose of BAY 1163877. The FU visit for subjects who either discontinue prematurely or finish dosing with BAY 1163877 will be performed 30 - 35 days after the last study drug treatment. There will be no long-term (survival) FU period.

Treatment: Subjects with PK assessment (all subjects of study Part 1 and 3 and at least 12 subjects of study Part 2 and approximately 8 subjects of the MTD expansion cohorts with impaired renal function at baseline) will receive BAY 1163877 (tablet or solution) on a continuous schedule starting with single-dose administration on Cycle 1, Day 1, followed by a "drugfree day" (to enable single dose PK assessments except for subjects in Part 3 who will receive BAY 1163877 twice daily continuously with no "drug free day"). Treatment with BAY 1163877 will resume on Day 3 of Cycle 1 if no protocol-defined dose-limiting toxicities (DLTs) are reported. Starting on Cycle 1,

Day 3, the study drug will be self-administered twice daily for the remaining 19 days of Cycle 1. For subsequent cycles, study drug will be administered twice daily for 21 days until disease progression or as long as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.

In one of the dose escalation cohorts in study Part 1 ("tablet bridging cohort"), relative bioavailability of the tablet formulation will be assessed by administration of a single dose of the tablet formulation on Cycle 1, Day -3. Starting with Cycle 1, Day 1, subjects enrolled in the "tablet bridging cohort" will continue with the solution formulation as described above. Depending on the results from the relative bioavailability assessment, subjects who initially start with solution formulation may be switched to tablet formulation in later cycles.

Approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2) will receive single doses of BAY 1163877 on Cycle 1, Day -3, after consumption of a high-fat, high-calorie breakfast and on Cycle 1, Day 1, after an overnight fast of at least 8 hours followed by treatment according to the schedule described above starting on Cycle 1, Day 3.

Subjects without PK assessment in study Part 2 will receive BAY 1163877 (tablet or solution) twice daily from Cycle 1, Day 1 ongoing.

At home, subjects will document the intake of study drug in a diary.

Subjects will continue receiving treatment until tumor progression, unacceptable toxicity, consent withdrawal, or subject withdrawal from the study at the discretion of the Investigator or his/her designated associate(s). As long as, in the judgment of the subject and the investigator, some benefit with evidence of tumor reduction or stable disease is being derived, dosing with BAY 1163877 may continue.

Determination of the MTD

An adaptive dose escalation design will be used to determine the MTD in study Part 1 (all comer). The MTD is defined as the highest dose that can be given such that not more than 20% of subjects experience a DLT during Cycle 1.

Without the occurrence of toxicities, dose escalation could be stopped and RP2D may be determined based on PK and/or PD results. The decision to continue treatment for an individual subjects will be made by the investigator according to the criteria specified in the protocol.

Each cohort will be evaluated after all subjects have completed the first 21 days of treatment (which will subsequently referred to as "Cycle 1") or early discontinued.

Safety monitoring will occur by telephone conferences with participation of the investigators and the sponsor on a regular basis.

At the time of dose escalation the available clinical safety information is discussed in a telephone conference by the involved investigators and representatives from the Sponsor including the Study Medical Expert as well as representatives of other clinical and if required further contributing functions (drug safety monitoring team – DSMT). During this telephone conference it will be judged if dose escalation can proceed as planned according to the procedure outlined below. Dose escalation for subsequent cohorts will only be considered after full evaluation of at least Cycle 1 safety data from the previous cohort.

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03) will be used to grade toxicities / adverse events.

The dose escalation will be performed as follows:

- Initially 3 subjects per dose level will be enrolled. In case 2 or more sites are conducting the dose escalation part, the initial enrolment of 4 subjects per dose level is optional.
- The starting dose of BAY 1163877 is 50 mg given as a single dose on Cycle 1, Day 1, and twice daily (b.i.d.) from Cycle 1, Day 3 (100 mg / day).
- The maximum dose escalation will be 2-fold.
- Possible daily doses of BAY 1163877 starting from 100 mg in increments of 100 mg.
- The possible maximum dose of BAY 1163877 is considered to be 550 mg b.i.d. (1100 mg / day). Higher doses might be explored after discussions between sponsor and investigators.
- If at least 1 subject out of 3 or 1 out of 4 in a cohort has DLTs or if at least 2 subjects report drug-related AEs (CTCAE v4.03) of Grade ≥ 2, any further dose escalation, de-escalation or cohort expansion will be decided in consultation between all investigator(s), and the sponsor (within the DSMT) after consideration of all available safety data of the previous cohorts. Any subsequent dose will be selected in order to determine the MTD.

  Model-based dose-response analysis of the DLT rates will be performed during these interim reviews in order to guide the dose decision. The model-based dose selection procedure is considering data at all dose levels (not just at the last cohort). The dose predicted to yield 20% DLT rates will be reported from that model as a best candidate for the next cohort.

  The final decision about the next dose will be made by the sponsor in consultation with all investigators (DSMT).

  If the selected dose is larger than the last dose tested, then escalation will be pursued. If it is lower, a de-escalation step will occur.

  Cohort expansion will occur when a previously tested dose is selected again for the next cohort of 3 subjects.

  Expansions at any given dose up to a total of 9 subjects are allowed. In principle, the selection of a next dose level where the predicted DLT rate is close to 20% should insure that the next dose tested will remain safe.

  Nevertheless, the following constraint will be added in order to protect subject safety during the adaptive dose selection decisions:

  - If 2 out of 3 (or 2 out of 4), at least 4 out of 6 (or at least 5 out of 9) subjects experience DLTs at a given dose level, only lower doses will be given in all subsequent cohorts because the probability that the dose is above the MTD is very large (above 95.4%).
  - The dose-escalation procedure will be stopped as soon as:

- the MTD has been defined with good precision (i.e. the coefficient of variation for the MTD is lower than or close to 40%)

  or

- at any time when the selected dose level for the next cohort has already been given in 9 subjects.

If the dose escalation stops, the sample size for the MTD cohort will be expanded up to a total of 20 evaluable subjects (study Part 1 / MTD expansion cohort (all comer)).

No intra-subject dose escalation is permitted. Dose interruptions and / or dose reductions may be required based on individual safety and tolerability.

Variables are specified in the Clinical Study Protocol[2].

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA), R release 2.4.1 or higher and BRugs release 0.3-3 or higher. All variables will be analyzed by descriptive statistical methods. The number of data available, mean, standard deviation, minimum, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

Data displays will follow the standard table catalogs for oncology standards, global standards, and clinical pharmacology standards, respectively.

The pharmacokinetic parameters will be evaluated statistically in accordance with pertinent company guidelines.

The following treatment groups will be analyzed.

In the following “XX mg” stands for the assigned dose.

Study Part 1: Dose escalation

- XX mg sol.
  - For regular dose escalation cohorts
- XX mg sol./tab. (and potentially XX mg tab./sol.)
  - For dose escalation cohorts related to bioavailability
- Total Dose Escalation

Study Part 1, Part 2 and Part 3 MTD Dose Expansion

- Exp.1 All Comers – XX mg tab.
- Exp.2 sqNSCLC – XX mg tab.

- Exp.2 LAC – XX mg tab.
- Exp.2 BC – XX mg tab.
- Exp.2 SCCHN – XX mg tab.

- Exp.3 sqNSCLC – XX mg tab.
- Exp.3 LAC – XX mg tab.
- Exp.3 BC – XX mg tab.

The categories of region used for subgroup analysis will be derived for each subject by using the variable country (location of the respective site).

4.2 Handling of Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been administered at least 1 dose of the study drug (BAY 1163877).

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see above) is regarded a "screening failure".

Subjects who discontinue due to a DLT will NOT be replaced.

Subjects who discontinue during the first cycle of therapy (Cycle 1) due to any reason other than a DLT and / or related toxicity, and subjects who took less than 80% of the required study drug (BAY 1163877) in Cycle 1 will be replaced to ensure 3 evaluable subjects per cohort for the determination of MTD and PK of BAY 1163877. Subjects who discontinue after the first cycle (Cycle 1) will not be replaced.

Subjects enrolled in Study Part 1 / MTD expansion (all comer) with insufficient paired biopsy samples will be replaced to ensure at least 10 subjects with paired biopsy samples for p-ERK1/2 analysis.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form (CRF).

Missing data will not be replaced. Possible impact of missing values on the analysis will be discussed in the clinical study report.

4.4 Interim Analyses and Data Monitoring

Safety data will be reviewed on an ongoing basis during study Part 1 / dose escalation (all comer). Bayesian dose-response and / or PK / PD modeling of DLTs rates and CTCAE v4.03 gradings may be performed after selected cohorts in order to generate additional relevant information for the adaptive dose selection decisions. The sponsor together with all investigators will review all available data and make the final decision as to dose escalation, de-escalation or cohort expansion

during the adaptive dose escalation part. This group will also determine when to implement predefined stopping rules.

No interim analysis is planned during dose expansion at MTD in study Part 1 (MTD expansion cohort "all comer"), study Part 2 (MTD expansion cohort "sqNSCLC + LAC+ BC + SCCHN") or study Part 3 (MTD expansion cohort "Safety cohort").

4.5 Data Rules

4.5.1 Baseline

Unless otherwise stated, baseline is defined as the last pre-dose assessment before first study drug administration or as the last pre-dose assessment before the time period being analyzed.

4.5.2 Unscheduled Measurements

If control measurements for a planned timepoint before study drug administration are available, the last value (i.e. of the measurement closest to the study drug administration) will be used for the calculation of descriptive statistics. If control measurements for a planned timepoint after study drug administration are available, the planned measurement will be used for the calculation of descriptive statistics.

Further applicable data rules are described in section 6 "Statistical Methodology".

4.6 Blind Review/Validity Review

The results of the validity review meeting will be documented in the Validity Review Report and may comprise decisions and details relevant for statistical evaluation. Any changes to the statistical analysis prompted by the results of the validity review meeting will be documented in an amendment and, if applicable, in a supplement to this SAP or will be documented in the clinical study report.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s) (see section 4.6).

Safety analysis set

All subjects who received at least 1 dose of BAY 1163877 will be included in the safety evaluation.

MTD analysis set

All subjects who completed Cycle 1 or discontinued during Cycle 1 due to an adverse event or DLT will be included in the MTD evaluation.

Efficacy analysis set

All subjects who received at least 1 dose of BAY 1163877 and who have post-baseline efficacy data available will be included in the efficacy evaluations.

Pharmacodynamic analysis set

All subjects with evaluable PD data and who complete the study without major changes versus protocol will be included in the evaluation of PD.

Pharmacokinetic analysis set

All subjects with valid pharmacokinetic data will be included in the evaluation of pharmacokinetic concentrations and parameters.

6. Statistical Methodology

The treatment groups to be analyzed are defined in section 4.1. The tables, listings, and figures will be separately displayed for the different parts of the study (i.e. Part 1 dose escalation, Part 1 MTD expansion cohort "all comer", Part 2 MTD expansion cohort "sqNSCLC + LAC+ BC + SCCHN", and Part 3 MTD expansion cohort "Safety cohort").

6.1 Population characteristics

Analyses for population characteristics will be performed for the safety population on the treatment groups if not stated otherwise. The results will be displayed by region (Asia, ROW, and total), if reasonable.

6.1.1 Disposition

Disposition at the end of screening will be summarized for subjects who signed the informed consent for FGFR testing and for all subjects who signed the main informed consent, respectively. Disposition at the end of Treatment and for the Safety follow-up will be summarized by treatment groups for all subjects assigned to treatment and the safety analysis set, respectively.

6.1.2 Protocol deviations

Frequency tables of protocol deviations by category and deviation coded term will be summarized by treatment group.

6.1.3 Demographics and other baseline characteristics

Demographics and general baseline characteristics will be summarized by treatment group. Quantitative data will be summarized by arithmetic mean, SD, median, minimum and maximum. Frequency tables will be provided for qualitative data. Variables include sex, race, ethnicity, age (as reported on the eCRF), weight, height, body mass index (BMI), and NYHA functional class.

Baseline cancer characteristics will be summarized by treatment group. Variables include for example baseline ECOG Performance Status, number of target lesions, number of non-target lesions, cancer type, histology, status of primary tumor, stage at initial diagnosis, grading at initial diagnosis, clinical status at study entry, stage at study entry, time since initial diagnosis. Please note that the list of the above mentioned parameters is not extensive.

In addition, demographics and baseline cancer characteristics will be summarized for all subjects who signed the informed consent for FGFR testing.

6.1.4 Prior and Concurrent Medication/Therapy

Prior anti-cancer therapy and surgical therapeutic procedures will be summarized by treatment group. The counts and percentages of patients who were previously treated using radiotherapy, local anti-cancer therapy, systemic anti-cancer therapy, and who had any diagnostic and therapeutic procedure(s) will be presented. The number of patients with radiotherapy and systemic or local anti-cancer therapy will be presented by intent of procedure and number of regimens/procedures. In addition, concurrent radiotherapy, diagnostic and therapeutic procedures will be summarized. Prior and concomitant medications will be coded to generic terms using the World Health Organization Drug Dictionary (WHO DD) Version 2017SEP or later and summarized by treatment group. The version used in analyses will be presented in the clinical study report.

6.1.5 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later. The version used in analyses will be presented in the clinical study report. Medical history data will be summarized by system organ class, high level term, and preferred term by treatment group.

6.2 Efficacy

Tumor response

Efficacy data, such as best tumor response, will be summarized using descriptive statistics and will be graphically displayed if appropriate. The correlation between PD parameters and selected safety, efficacy, or PK parameters may be graphically displayed. Further statistical analyses may be conducted.

The efficacy analysis will include descriptive analyses on response rate, progression-free survival (PFS), time to progression (TTP), overall survival (OS), duration of response (DOR), duration of stable disease (DOSD), and duration of treatment (DOT).

Response as defined by RECIST v.1.1: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). Response and progression will be evaluated in this trial using the new international criteria proposed by the RECIST committee for solid tumor.

OS is defined as the time (days) from the date of first dose of study drug to death due to any cause. Subjects alive at the time of analysis will be censored at the last contact date. OS for subjects without any contact after first dose of study drug will be censored at 1 day.

PFS is defined as the time (days) from the date of the first dose of study drug to the date of the first observed disease progression (radiological or clinical) or death due to any cause, if death occurs before progression is documented. PFS for subjects without tumor progression at the time of analysis will be censored at their last date of tumor evaluation.

TTP is defined as the time from start of study treatment until first observed disease progression (radiological or clinical). In comparison to PFS, TTP does not consider death as an event.

DOR (for partial and complete response (PR/CR)) is defined as the time (days) from the first documented objective response of PR or CR, whichever is noted earlier, to disease progression or death (if death occurs before progression is documented).

DOSD is defined as the time (days) from start of study treatment to date that disease progression or death (if death occurs before progression) is first documented.

Kaplan-Meier (KM) product-limit estimates for median, 25th and 75th percentile with its 95% CI together with total number of subjects, total censored and total events will be provided for PFS and TTP per treatment. In addition KM survival curves will be presented for each treatment group.

Best overall tumor response according to RECIST criteria will be summarized by treatment group and region (Asia, ROW, and total) using frequency counts.

Best % Change in Target Lesion sum of diameter from Baseline will be displayed graphically for all subjects from worst to best in a waterfall plot.

Subgroup analysis will be performed by prior immunotherapy information (prior immunotherapy vs. no prior immunotherapy) .

6.3 Pharmacokinetics/pharmacodynamics

6.3.1 Pharmacokinetics

The concentration-times courses of all analytes will be tabulated for each cohort by treatment. The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation, and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms), and CV, minimum, median, maximum value, and the number of measurements. Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value, a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Individual and geometric mean concentration vs. time curves of all analytes (using the actual sampling times for individual plots and the planned sampling times for mean plots) will be plotted by cohort using both linear and semilogarithmic scale.

The amount and percent of drug excreted into urine will be graphically illustrated for the sampling interval as well as for the whole sampling period (bar-charts for the individual data and the arithmetic mean including standard deviation).

Pharmacokinetic characteristics ($t_{max,}$ $t_{last,}$ and %AUC(t_{last} - ∞) excluded) will be summarized by the statistics mentioned above. t_{max} and t_{last} will be described utilizing minimum, maximum, and median as well as frequency counts.

PK Dose proportionality

To investigate dose proportionality, an explorative ANOVA, including the factor cohort, will be performed on the log-transformed values of C_{max}/D, AUC(0-t_{last})/D, and AUC/D calculated from single (where applicable) and multiple dose PK profiles.

Bridging: tablet vs solution relative bioavailability

PK parameters of different dose levels will be analyzed together for the assessment of relative bioavailability.

In order to evaluate the relative bioavailability of the tablet formulation, tablet C_{max}/D, AUC(0-t_{last})/D, and AUC/D on Cycle 1, Day -3 will be compared to solution C_{max}/D, AUC(0-t_{last})/D, AUC/D on Cycle 1, Day 1 for all analytes. If needed, additional PK parameters may be used for relative bioavailability assessment. The logarithms of these PK parameters will be analyzed using analysis of variance (ANOVA) including subject and formulation effects.

Based on these analyses, point estimates (LS-means) and exploratory 90% confidence intervals for the ratios (tablet/solution) of C_{max}/D, AUC(0- t_{last})/D, and AUC/D will be calculated by re-transformation of the logarithmic data using the intra-individual standard deviation of the ANOVA.

Subjects to be included in the relative bioavailability evaluation ("tablet bridging cohort") should have evaluable pharmacokinetic data on both Cycle 1, Day -3 and Cycle 1, Day 1.

Food effect

In order to evaluate the effect of food on BAY 1163877, C_{max} and AUC(0-t_{last}) on Cycle 1, Day -3 and C_{max} and AUC(0-t_{last}) on Cycle 1, Day 1 will be compared. The logarithms of C_{max} and AUC(0-t_{last}) will be analyzed using ANOVA including subject and food effect.

Based on these analyses, point estimates (LS-means) and exploratory 90% confidence intervals for the ratios (high-fat, high-calorie meal / fasting) of C_{max} and AUC(0- t_{last}) will be calculated by re-transformation of the logarithmic data using the intra-individual standard deviation of the ANOVA.

The PK paramteres C_{max}/D, AUC(0-t_{last})/D, AUC/D, C_{max}. and AUC(0-t_{last}) will be graphically illustrated using stickplots. Scatterplots of the PK parameters C_{max}/D, AUC(0-t_{last})/D, AUC/D will be created.

6.3.2 Pharmacodynamic data

Cardiovascular parameters will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented by cohort for the original data as well as for the difference to baseline (defined as the pre-dose assessment of the day being analyzed).

Graphical displays of individual data as well as mean values with standard deviation will be included for absolute values as well as change from baseline.

6.4 Safety

The results will be displayed by region (Asia, ROW, and total), if reasonable.

6.4.1 Study drug exposure

Duration of treatment will be summarized using summary statistics. Actual dose, total amount of dose, and percent of planned dose during study period will be also summarized. Dose modification with reason will be summarized.

6.4.2 Maximum tolerated dose

Individual listings and treatment summaries of DLTs with CTCAE v4.03 code and grade will be presented.

The incidence of subjects with DLTs during Cycle 1 will be summarized by treatment and, as possible, modeled as a function of BAY 1163877 dose using Bayesian logistic regression. The moderately-informative independent priors used during the interim dose response analysis (see Section 6.5 for details) as well as non-informative priors will be used for this analysis to assess sensitivity of the estimates. Parameter estimates and model predictions will be reported with 90% credibility sets. The MTD will be computed as a derived function of model parameters as:

$$MTD = (\log(0.2/0.8)\text{-intercept})/\text{slope}.$$

The posterior distribution of the MTD will be summarized in tabular and graphical formats.

6.4.3 Adverse Events

Adverse events will be analyzed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) version 4.03. In addition a separate set of AE tables will be generated using MedDRA terms.

The incidence of treatment-emergent adverse events (TEAEs), drug-related adverse events (TEADRs), treatment-emergent and drug-related serious adverse events (SAEs), respectively, will be summarized by treatment arm, cohort, CTCAE body system code and worst NCI-CTCAE grade. TEAEs, SAEs, drug-related TEAEs, and drug-related SAEs for events of Grade 3/4/5 will be summarized similarly.

AEs are considered treatment emergent if they have started or worsened after the first study drug administration up to 30 days after the end of treatment with study drug.

Frequency tables will also be provided for the changes of CTCAE grade from pre-treatment and changes of worst CTCAE grade under treatment.

In addition, TEAEs, SAEs, drug-related TEAEs, and drug-related SAEs will be summarized by MedDRA (Version 20.1 or later) system organ class, preferred term and worst NCI-CTCAE grade. The same will be also summarized similarly for events of Grade 3/4/5.

Patient listings of all AEs, SAEs, AEs leading to dose reduction, AEs leading to dose interruption, AEs leading to discontinuation, dose limiting toxicity AEs, and deaths will be presented.

6.4.4 Safety Parameters

Quantitative data (vital signs, ECG, ECOG performance status) will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum, and maximum. These summary statistics will be presented by treatment arm and cohort for the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data. Graphical displays of mean values with standard deviation will be provided.

The average of triplicate quantitative ECG parameters at all ECG time points will be used for all analyses.

Laboratory data outside the reference range will be listed and flagged with 'L' for low and 'H' for high. The incidence of laboratory data outside the reference range (low, high) will be summarized by treatment arm and cohort in frequency tables.

Calcium, phosphate and the product of calcium and phosphate will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented by cohort for the original data as well as for the difference to baseline (defined as the pre-dose assessment of the day being analyzed).

Graphical displays of mean values with standard deviation will be included for absolute values as well as change from baseline.The number of subjects with at least one phosphate level > 5.5 mg/dL, with at least one phosphate level > 7 mg/dL and with at least one phosphate level > 9 mg/dL will be summarized using frequency tables.

The number of subjects with at least one value > 70 mg^2/dL^2 of the product phosphate and calcium will be summarized using frequency tables.

The incidence of laboratory toxicities will also be summarized by worst CTCAE v4.03 grade and by treatment group and cohort. Frequency tables will also be provided for the changes of worst CTCAE v4.03 grade after start of treatment versus baseline.

6.5 Interim dose response modeling

The following Bayesian dose-response analysis of the DLT rates will be performed during the interim reviews in order to guide the dose escalation decision.

Bayesian logistic regression

The analysis is based on a method reported by Tibaldi et al.[3]

A range of doses will be tested, including possibly 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 and 1100 mg. Additional or alternative dose levels may be chosen. These possible dose levels are labeled as $d = 1, \ldots, N$, where N is the maximum number of dose levels for the study. The probability, p, of observing a subject with DLTs during Cycle 1 is modeled as a function of dose:

$$\log\left(\frac{p}{1-p}\right) = \text{intercept} + \text{slope} * d$$

In this trial, the MTD is defined as the predicted dose where the DLT probability is 20%:

$$\text{MTD} = (\log(0.2/0.8)\text{-intercept})/\text{slope}.$$

A Bayesian analysis will be performed, considering the following independent priors for the model parameters:

- intercept has a normal distribution with mean equal to -3 and variance equal to 1.
- slope has a positive normal distribution with mean equal to 0.0015 and variance equal to 0.003.

These priors were specified in the protocol. They are moderately-informative and were considered plausible in the context of the current dose escalation scheme and indication.

The posterior distribution of model parameters and the MTD will be estimated with the R package BRugs using MCMC techniques and considering at least 10000 simulations after convergence of the Markov chain.

The precision of the MTD will be monitored by calculating the relative median absolute difference (RMAD% = 100*mad/median). This robust estimator is a suitable statistic to quantify variability in asymmetric distributions. A low RMAD(MTD)% value indicates good precision.

In addition, the following posterior probabilities will be calculated for each dose level in the candidate set:

- Td = (tolerable) Probability that the DLT rate is below 0.20, Pr(p <0.20| d), for a dose d.
- Qd = Probability of dose d being the MTD. This is the probability that d is the maximum dose from the candidate set where p<20%.

Guidance for selection of next dose

The posterior density of the MTD and the Qd probabilities in the candidate set are the two main instruments that will be reported to guide dose selection. They indicate on a continuous and discrete scale respectively the desirability for a dose to become the next choice. The larger the value, the more likely the corresponding dose is the MTD.

We recommended to compare the desirability of various dose candidates prior to making the dose selection decision. Doses with a high desirability are more likely to be the MTD, so they are preferred. When several doses have a similarly high desirability value, they are equally likely to become the MTD and the choice may be driven by other factors.

To avoid over dosing, only doses at most 2-fold larger than the maximum dose tested can be considered as candidates for the escalation process.

Guidance for stopping the dose escalation

Four indicators will be monitored and the dose escalation process may be terminated as soon as either statistic has reached a target threshold, as defined in the protocol.

1. MTD precisely estimated: CV(MTD) calculated as the inter-quartile range over the median is lower than 40%.
2. Maximum possible dose is safe T_N >80%.
3. Minimum dose tested (100 mg) is toxic (T_1 <20%).

4. Total sample size for next dose is already equal to 9.

Criteria 1. to 3. will end up in a conclusive dose escalation study. The conclusion will be either that 1. the MTD has been found , 2. all doses are safe or 3. they are all toxic. Criterion 4. does not lead to any interpretation about DLTs but it is a practical constraint to limit the overall duration of the study.

7. Document history and changes in the planned statistical analysis

- Approval of SAP, Version 1.0, 22 Mar 2018

8. References

[1] Investigator's Brochure BAY 1163877 (Rogaratinib), Version 8.0, dated 10 Oct 2017.

[2] Integrated Clinical Study Protocol No. 1163877 / 16443, Version 7.0, dated 16 Mar 2017.

[3] Tibaldi FS, Beck BH, A. B. Implementation of a Phase 1 adaptive clinical trial in a treatment of type 2 diabetes. Drug Inf J. 2008;42(5):455-65.