Document Type:	Study Protocol
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
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Cover page of the integrated protocol

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

This protocol version is an integration of the following documents / sections:

- **Original protocol,** Version 1.0, dated 25 Jul 2013
- **Amendment no. 1** (described in Section 15.1)
  forming integrated protocol Version 2.0, dated 31 Oct 2013
- **Amendment no. 2** (described in Section 15.2)
  forming integrated protocol Version 3.0, dated 19 Mar 2014
- **Amendment no. 3** (described in Section 15.3)
  forming integrated protocol Version 4.0, dated 19 Jun 2014
- **Amendment no. 4** (described in Section 15.4)
  forming integrated protocol Version 5.0, dated 31 Oct 2014
- **Amendment no. 5** (described in Section 15.5)
  forming integrated protocol Version 6.0, dated 19 Sep 2016
- **Amendment no. 7** (described in Section 15.6)
  forming integrated protocol Version 7.0, dated 16 Mar 2017
- **Amendment no. 9** (described in Section 15.7)
  forming integrated protocol Version 8.0, dated 17 Oct 2018.

This document integrates the original protocol and all global amendments.

Amendments not included in the consecutive numbering of amendments above are local amendments not forming part of this integrated global protocol. This currently includes:

- **Amendment no. 6** (local amendment for US only), dated 06 Dec 2016
- **Amendment no. 8** (local amendment for South Korea only) dated 30 Oct 2017

1 Title page - amended

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

Test drug:	BAY 1163877 / pan-FGFR inhibitor		
Study purpose:	To determine the maximum tolerated dose (MTD)		
Clinical study phase:	**I** (first-in human)	**Date:**	17 Oct 2018
EudraCT no.:	**2013-002155-15**	**Version no.:**	8.0
Study no.:	BAY 1163877 / 16443		
Sponsor:	**Sponsor (Non-US): Bayer AG, D-51368 Leverkusen, Germany** **Sponsor (US territory): Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA**		
Sponsor's medical expert: [1]	PPD Bayer AG Muellerstrasse 178, 13353 Berlin, Germany Phone No: PPD		

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

[1] The medical expert changed, see Amendment 7, see section 15.6.2.1

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the clinical study protocol as presented.

PPD	
Name	Role
30-OCT-2018	PPD
Date	S

[2] The medical expert changed with Amendment 7

Signature of coordinating / principal investigator

The signatory agrees to the content of the clinical study protocol as presented.

Name	Role
Date	Signature

2 Synopsis - amended

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
Short title	Phase I dose escalation pan-FGFR inhibitor
Clinical study phase	I (first-in human)
Project number	445410
Study objective(s)	**Primary objectives** 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 **Secondary objectives** To evaluate biomarker status, pharmacodynamic (PD) parameters and tumor response **Exploratory objective**[3] To evaluate selected immune parameters
Test drug(s)	BAY 1163877
Name of active ingredient	BAY 1163877
Formulation IMP 1	Ready-to use solution for oral application (10 mg BAY 1163877 per 1 mL solution)
Formulation IMP 2	Tablet (50 mg tablet and 200 mg tablet)

[3] Exploratory objective added by Amendment 7, see section 15.6.2.2

Dose(s)	*Study Part 1 / dose escalation (all comer)* • Starting dose: 50 mg once on Cycle 1, Day 1 (single dose) 50 mg twice daily (b.i.d. = bis in die) from Cycle 1, Day 3 (100 mg / day) ongoing *Study Part 1 / MTD expansion (all comer)* • Subjects receive the MTD of BAY 1163877 determined at the end of dose escalation. *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN):* • Subjects receive the MTD of BAY 1163877 determined in study Part 1. *Study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC):* • Subjects receive the MTD of BAY 1163877 determined in study Part 1.[4]
Route of administration	Oral (p.o.)
Duration of treatment	Duration and dosing schedule for subjects participating in PK assessments (all subjects of study Part 1 and at least 12 subjects of study Part 2): Subjects will receive BAY 1163877 (tablet or solution) on a continuous schedule starting with single-dose administration on Cycle 1, Day 1, followed by a "drug-free day" (to enable single dose PK assessments). 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 each Cycle. Duration and dosing schedule of subjects enrolled for tablet relative bioavailability assessment ("tablet bridging cohort") of study Part 1:

[4] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.2

Duration of treatment (continued)	Subjects will receive a single dose of tablet formulation on Cycle 1, Day -3, and then continue with the solution formulation starting on Cycle 1, Day 1, according to the schedule described above. Duration and dosing schedule of subjects enrolled for food effect assessment in the MTD expansion cohorts of study Part 1 and Part 2: 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. Duration and dosing schedule for subjects of study Part 2 without PK assessment: Subjects will receive BAY 1163877 (tablet or solution) twice daily from Cycle 1, Day 1 ongoing. Evidence of tumor progression, unacceptable toxicity, consent withdrawal or subject's withdrawal from the study at the discretion of the Investigator may lead to termination of treatment. Duration and dosing schedule for subjects of study Part 3: Subjects will receive BAY 1163877 twice daily from Cycle 1, Day 1 ongoing. Evidence of tumor progression, unacceptable toxicity, consent withdrawal or subject's withdrawal from the study at the discretion of the Investigator may lead to termination of treatment.[5]
Reference drug (s)	Not applicable
Indication	Refractory, locally advanced or metastatic solid tumors

[5] Part 3 was added by Amendment 7, see section 15.6.2.2

Diagnosis and main criteria for inclusion	Inclusion criteria: Eligibility criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 1, Part 2, and Part 3)[6] • Ability to understand and willingness to sign the written subjects information sheet / informed consent form (SIS / ICF) for FGFR expression / FGFR mutation testing. Signed informed consent (IC) has to be obtained before any study specific procedure. • Subjects with histologically or cytologically confirmed, refractory, locally advanced or metastatic solid tumors (all comer for study Part1; sqNSCLC, LAC, BC or SCCHN for Part 2; sqNSCLC, LAC, or BC for Part 3) who are not candidates for standard therapy. [7] • Male or female subjects ≥ 18 years of age • Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2 • Life expectancy of at least 3 months • Existence of archival or fresh tumor biopsy specimen for FGFR expression / FGFR mutation testing Besides these basic criteria, any criterion as outlined below already known to prohibit the patient's participation in the study should be considered. Eligibility criteria for study treatment • Ability to understand and willingness to sign the written SIS / ICF for study treatment eligibility. • Signed informed consent (IC) obtained before any (further) study specific procedure. • Subjects with histologically or cytologically confirmed, refractory, locally advanced or metastatic solid tumors who are not candidates for standard therapy. Subjects with any type of solid tumors (all comer)

6 Part 3 was added by Amendment 7, see section 15.6.2.2

7 Part 3 was added by Amendment 7, see section 15.6.2.2

Diagnosis and main criteria for inclusion (continued)	will be eligible for dose escalation and dose expansion at MTD in Part 1. • Subjects enrolled in the MTD expansion cohorts of Study Part 1, Part 2, and Part 3 must present high FGFR expression levels based on archival or fresh tumor biopsy specimen analysis. Bladder cancer subjects with low overall FGFR expression levels can be included if activating FGFR3 mutations are confirmed. **(only for MTD expansion cohorts of study Part 1 (all comer), Part 2 (sqNSCLC + LAC +BC + SCCHN)) and Part 3 (sqNSCLC + LAC + BC)**[8] • Subjects must have at least one measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. A lesion in a previously irradiated area is eligible and to be considered as measurable disease as long as there is objective evidence of progression of the lesion prior to study enrollment. • Subjects with resected primary tumors who have documented metastases are eligible. • Subjects consent to undergo a paired biopsy at screening and on Cycle 2, Day 1 **(only for MTD expansion cohorts of study Part 1 (all comer))** Note: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy for biomarker (p-ERK1/2) studies is taken.[9] Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies. • Only for study Part 3: Subjects consent to undergo a paired biopsy at screening and between Cycle 2, Day 1 and Cycle 2, Day 21[10]

[8] Part 3 was added by Amendment 7, see section 15.6.2.2

[9] Amended by Amendment 7, see section 15.6.2.2

[10] Part 3 was added by Amendment 7, see section 15.6.2.2

Diagnosis and main criteria for inclusion (continued)	• Male or female subjects ≥ 18 years of age • Life expectancy of at least 3 months • Recovery to National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE v4.03) Grade 0 or 1 level or recovery to baseline preceding the prior treatment from any previous drug / procedure-related toxicity (subjects with persistent alopecia, anemia, and / or hypothyroidism can be included). • Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2 • Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting the study treatment: • Absolute neutrophil count (ANC) ≥ 1,500/mm^3 • Platelet count ≥ 75,000/mm^3 • Total bilirubin ≤ 1.5 times the upper limit of normal (ULN). Documented Gilbert syndrome is allowed if total bilirubin is mildly elevated (< 6 mg/dL). • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (≤5 x ULN for subjects with liver involvement of their cancer) • Alkaline phosphatase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer) • Lipase ≤ 5 x ULN – Not more than Child-Pugh score B7 hepatic impairment – Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 according to the modified diet in renal disease (MDRD) abbreviated formula • International normalized ratio (INR) ≤ 1.5 x ULN and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN. Subjects being treated with anticoagulant, e.g. warfarin or heparin, will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. Close monitoring of at least weekly evaluations will be performed until INR is stable based on a pre-dose measurement as defined by the local standard of care.

Diagnosis and main criteria for inclusion (continued)	• Subjects with a history of hypertension should be on stable anti-hypertensive medicine for more than 7 days before start of study treatment. • Women of childbearing potential and men must agree to use adequate contraception before entering the program until at least 8 weeks after the last study drug administration. The investigator or a designated associate is requested to advise the subject on how to achieve an adequate birth control. Adequate contraception is defined in the study as any medically recommended method (or combination of methods) as per standard of care. • Women of childbearing potential must have a pregnancy test performed a maximum of 7 days before start of study treatment, and a negative result must be documented before start of study treatment.
Study design	Phase I, first-in-human, open-label, non-randomized, multi-center, 2-part, dose-escalation / dose-expansion study of BAY 1163877 in sequential cohorts of subjects with refractory, locally advanced or metastatic solid tumors. Study Part 1 will identify the maximum tolerated dose (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. Part 2 may start as soon as the MTD has been established in Part 1. Study Part 3 will expand the safety database and in parallel will collect additional efficacy data and explore changes of selected immune parameters during treatment with BAY 1163877 at the MTD identified in Part 1 in subjects with sqNSCLC, LAC, and BC.[11]

[11] Part 3 added by Amendment 7, see section 15.6.2.2

Methodology	Eligible cancer subjects will be enrolled at multiple centers worldwide. In total, the "on study" period for the subjects comprises 3 phases: • Pre-treatment – FGFR expression / FGFR mutation testing – 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 long 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 long as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs. *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.[12]

[12] Part 3 added by Amendment 7, see section 15.6.2.2

Methodology (continued)	*MTD expansion cohorts (study Part 1 and Part 2) / "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. 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[13]) can run in parallel. • Follow-up (FU) End of Treatment (EOT) visit 0-14 days after last dose of BAY 1163877 Follow-up (FU) visit 30-35 days after last dose of BAY 1163877 At home, subjects will document the intake of study drug (date and time of dosing as well as the administered dose) on a compliance sheet / paper diary (source document to verify treatment compliance). The complete duration of the study (Part 1, Part 2 and Part 3)[13] depends on the number of dose-escalation steps in Part 1 and will be approximately 7 years.

[13] Part 3 added by Amendment 7, see section 15.6.2.2

Methodology (continued)	**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. 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. 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 drug safety monitoring team = 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 (see details in Section 16.4). 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.

Methodology (continued)	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 patient will be made by the investigator according to the criteria specified in the protocol (Section 8.4). 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.

Methodology (continued)	**Pharmacokinetics (PK):** Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 (up to 48 hours after dosing) in the "tablet bridging cohort", and on Cycle 1, Day 1 (up to 48 hours after dosing) and on Cycle 1, Day 15 (up to 12 hours after dosing), respectively, in all subjects participating in Study Part 1 (all comer) and in at least 12 subjects participating in Study Part 2 (sqNSCLC + LAC + BC + SCCHN). In all subjects participating in Study Part 3, multiple dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day 15 (up to 12 hours after dosing).[14] In approximately 8 subjects enrolled in MTD expansion cohorts (study Part 1 and Part 2), single dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 (up to 48 hours after dosing) and on Cycle 1, Day 1 (up to 48 hours after dosing) for food effect assessment. In the MTD expansion cohorts, in approximately 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated formula), serial PK blood samples will be collected on Cycle 1 Day 1 and Day 15.[15] Plasma concentration of BAY 1163877 will be measured using a validated method. In approximately 8 subjects enrolled in MTD expansion cohorts (study Part 1 and Part 2), urine will be collected for 24 hours after dosing on Cycle 1, Day 1 (concurrently with plasma PK samples) and analyzed using validated method. Exploratory monitoring of metabolites may also be performed in pooled plasma (most likely at the MTD or the therapeutic dose) and urine samples.

[14] Part 3 added by Amendment 7, see section 15.6.2.2

[15] Modified by Amendment 7, see section 15.6.2.2

Methodology (continued)	**Safety / tolerability:** Safety will be assessed by close monitoring and timely assessment of adverse events (AEs), laboratory parameters (blood tests, urinalysis), vital signs (blood pressure, heart rate), subject's medical condition (physical examination including weight), ophthalmological examination, general well-being and activities of daily life (Eastern Cooperative Oncology Group (ECOG) performance status).[16] Each subject will be regularly assessed in each cycle for potential AEs and disease related signs and symptoms. The CTCAE v4.03 will be used to grade toxicities / AEs. **Cardiovascular assessment:** Blood pressure (BP) and heart rate (HR) will be measured at screening, frequently on PK profile days in Cycle 1, and once at all other visits during treatment and follow up. **Electrocardiogram (ECG):** 12-lead ECG readings will be performed at screening, on Cycle 1, Days -3 and -2 ("tablet bridging cohort" and "food effect assessment" only), on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle, and at the EOT visit. **Pharmacodynamic (PD) biomarkers:** In an attempt to demonstrate the mechanism of action of BAY 1163877, biomarkers will be studied in tissue samples. **Biomarker analysis in tumor tissue** Biomarker analysis will be done at screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN; Part

[16] Amended by Amendment 7, see section 15.6.2.2

Methodology (continued)	3: *"Safety cohort" sqNSCLC + LAC + BC*) according to FGFR expression levels / FGFR mutation using either an archival or fresh tumor biopsy material (see inclusion criteria).[17] Analysis of phospho-extracellular signal-regulated kinase 1/2 levels, (p-ERK1/2) will be done at screening and on Cycle 2, Day 1 for all subjects of study Part 1 and Part 2 who are willing to undergo a biopsy both at screening and on Cycle 2, Day 1.[18] Both biopsies are mandatory for "all comer" subjects included in the MTD expansion cohort of Part 1. Priming of immune response (only in Part 3 "Safety cohort"): Selected parameters of immune response will be measured in fresh tumor tissue at baseline and between Cycle 2, Day 1 and Cycle 2, Day 21 and peripheral blood at the following timepoints: at baseline; Cycle 1, Day 8; Cycle 2, Day 1; Cycle 2, Day 15; and on the day of the second biopsy.[19] **Tumor response evaluation:** Computed tomography (CT) or magnetic resonance imaging (MRI) of all anatomic regions involved with the disease will be performed at screening (baseline), at the end of Cycle 2 and thereafter, every third cycle to assess tumor response using the Response Evaluation Criteria in Solid Tumors, Version 1.1. (RECIST v1.1)(1). **Recommended Phase II dose (RP2D):** The RP2D will be determined at the end of the study (after Part 2).
Type of control	The study is uncontrolled.
Number of subjects	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. • *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

[17] Part 3 added by Amendment 7, see section 15.6.2.2

[18] 'Study Part 1 and Part 2' added by Amendment 7

[19] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.2

	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.
Number of subjects (continued)	• *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)*: Additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and a cohort of at least 30, up to a maximum of 50 evaluable subjects with BC and at least 8 subjects with SCCHN treated at MTD.[20] • 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.[21]
Primary variables	Determination of MTD The primary variable for MTD determination will be the incidence of DLTs during the first 21 days of treatment (Cycle 1). The primary study outcome is the MTD being defined as the maximum dose at which the incidence of DLTs during Cycle 1 is below 20%. Pharmacokinetics: (BAY 1163877) **On Cycle 1 Day -3 ("tablet bridging cohort" and "food effect assessment" only) and Cycle 1, Day 1:** C_{max}, AUC(0-12), AUC(0-t_{last}), AUC and corresponding dose adjusted parameters (C_{max}/D, AUC(0-12)/D AUC(0-t_{last})/D, AUC/D and AUC). Amount of BAY 1163877 excreted renally during 0 to

[20] Modified by Amendment 6, see section 15.6.2.2

[21] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.2

	12 h ($A_{E,ur}$(0-12)), 12 to 24 h ($A_{E,ur}$(12-24)) and 0 to 24 h ($A_{E,ur}$(0-24)) post-dose will be calculated at the MTD and also expressed as percent of dose administered. **For Cycle 1, Day 15:** $C_{max,md}$, C_{max}/D_{md}, $AUC(0\text{-}12)_{md}$, $AUC(0\text{-}12)/D_{md}$, $AUC(0\text{-}t_{last})_{md}$, and $AUC(0\text{-}t_{last})/D_{md}$.
Plan for statistical analysis	This is primarily a descriptive safety and tolerability trial. A confirmatory analysis is not intended. Quantitative data will be described by summary statistics. Frequency tables will be provided for qualitative data. The incidence of subjects with DLTs during Cycle 1 will be summarized by cohort and, as possible, modeled as a function of BAY 1163877 dose using Bayesian logistic regression to guide the dose selection. PK data will be summarized by descriptive statistics. To investigate dose proportionality, bioavailability and food effect, ANOVA will be performed on the log-transformed values of appropriate PK parameters and 90% confidence intervals will be derived.

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List of abbreviations

%AUC(t_{last}-∞)	percentage of AUC from the last data point > LLOQ to infinity
AE	adverse event
$A_{E,ur}$(0-12)	amount of drug excreted via urine during the collection interval 0 – 12 hours post administration
$A_{E,ur}$(0-24)	amount of drug excreted via urine during the collection interval 0 – 24 hours post administration
$A_{E,ur}$(12-24)	amount of drug excreted via urine during the collection interval 12 – 24 hours post administration
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
anti-HCV	hepatitis C virus antibodies
anti-HIV	human immunodeficiency virus antibodies
AP	alkaline phosphatase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration vs time curve from zero to infinity after single (first) dose
AUC(0-12)	AUC from time zero to 12 hours p.a. after first-dose administration
$AUC(0\text{-}12)_{md}$	AUC(0-12) after multiple-dose administration
AUC(0-t_{last})	AUC from time zero to the last data point > LLOQ
AUC/D	AUC divided by dose
AUC_{norm}	area under the curve divided by dose per kg body weight
b.i.d.	twice daily (bis in die)
BC	bladder cancer
BMI	body mass index
BP	blood pressure
bpm	beats per minute
Ca	calcium
CI	confidence interval
CK	creatine phosphokinase
CLcr	creatinine clearance
C_{max}	maximum drug concentration in plasma after first dose administration
$C_{max,md}$	C_{max} after multiple-dose administration

$C_{max,norm}$	maximum drug concentration in plasma after single dose administration divided by dose (mg) per kg body weight
C_{max}/D	maximum drug concentration in plasma after single dose administration divided by dose
CPK	creatine phosphokinase
CRA	clinical research associate / assistant
CRO	contract research organization
CRP	C-reactive protein
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE v 4.03	Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (CTCAE v4.03: June 14, 2010) of the National Cancer Institute (NCI), U.S. Department of Health and Human Services, National Institutes of Health
C_{trough}	drug concentration in plasma at the end of the dosing interval
CV	coefficient of variation
d	dose
Diary	paper diary
DLT	dose limiting toxicity
DSMT	drug safety monitoring team
E(p|d)	posterior mean probability of DLT for dose d.
e.g.	exempli gratia, for example
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data collection / capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGF23	fibroblast growth factor 23
FGFR	fibroblast growth factor receptor
FGFR1/2/3/4	FGFR tyrosine kinases 1/2/3/4
FU	follow-up
GCP	good clinical practice
GFR	glomerular filtration rate

GMP	good manufacturing practice
GOT	glutamic oxaloacetic transaminase (=AST)
GPT	glutamic pyruvic transaminase (=ALT)
Hb	hemoglobin
HBDH	lactate dehydrogenase-1 isoenzyme (hydroxybutyrate dehydrogenase)
HBsAg	hepatitis B surface antigen
HDL	high-density lipoprotein
HDPE	high density polyethylene
HFSR	hand-foot skin reaction
HIV	human immunodeficiency virus
HR	heart rate
i.e.	id est, that is
IB	investigator's brochure
ICH	International Conference of Harmonization
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalized ratio (reagent-independent prothrombin ratio)
IRB	institutional review board
ISF	investigator site file
IVRS	Interactive voice response system
IWRS	Interactive web response system
kg	kilogram
K-ras	Kirsten rat sarcoma 2 viral oncogene homologue (cancer gene wild type)
L	liter
LAC	lung adenocarcinoma
LAP	leucine aminopeptidase
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LPFV	last patient first visit
LPLV	last patient (subject) last visit
LVEF	left ventricular ejection fraction
MABEL	minimum anticipated biological effect level
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration

MCV	mean corpuscular volume
md	multiple dose
MDRD	Modification of Diet in Renal Disease (equation)
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
mmHg	millimeter of mercury
MRI	magnetic resonance imaging
msec	millisecond
MTD	maximum tolerated dose
MUGA	multiple gated acquisition scan
NCA	non-compartmental analysis
NCI	National Cancer Institute
NIMP	non-investigational medicinal product
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
p.d.	post-dose
p.o.	per os (by mouth, orally)
PCHE	plasma cholinesterase
PD	pharmacodynamic
PD	progressive disease
PD-L1	programmed death-ligand 1
p-ERK	phospho-extracellular signal–regulated kinase
p-FGF	phospho-fibroblast growth factor
pFRS	p-FGF receptor substrate
PFS	progression-free survival
PK	pharmacokinetic(s)
PO4	phosphate
popPK	population PK (models)
PR	PR interval in ECG
PTF	peak trough fluctuation
PT-INR	international normalized ratio for prothrombin time
PTT	partial thromboplastin time
QA	quality assurance
QC	quality control
Qd	probability of dose d being the MTD
QRSD	QRS duration
QT	QT interval in ECG

QTc	QT interval corrected for heart rate
RBC	red blood count
RECIST v1.1	Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1
ROS	Roll-over study
RP2D	recommended Phase II dose
SAE	serious adverse event
SAS	statistical analysis system
SCCHN	squamous cell carcinoma of the head and neck
sd	standard deviation
SD	stable disease
sec	second
SIS / ICF	subject information sheet / informed consent form
SNR	screening number
SOP	standard operating procedure
SPC	summary of product characteristics
sqNSCLC	squamous non-small cell lung cancer
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life associated with the terminal slope
Td	(tolerable) probability that the DLT rate is below 0.20, Pr(p <0.20| d), for a dose d
TEADR(s)	treatment-emergent drug-related adverse event(s)
TEAE(s)	treatment-emergent adverse event(s)
t_{last}	time of last plasma concentration above LLOQ
t_{max}	time to reach maximum drug concentration in plasma after single (first) dose
$t_{max,md}$	time to reach maximum drug concentration in plasma after multiple-dose administration
TNM	tumor node metastasis (classification)
TSH	thyroid stimulating hormone (thyrotropin)
TTP	time to progression
ULN	upper limit of norm (upper limit of normal laboratory values)
USA	United States of America
V	apparent volume of distribution
vs.	versus
V_{ss}/F	apparent volume of distribution at steady state after extravascular administration
V_z/F	apparent volume of distribution during terminal phase after oral administration

WBC	white blood cell (count)

Definitions of terms

Progression-free survival (PFS)	Time (days) from the date of the first dose of study drug to the date of the first observed radiological disease progression or death, whatever comes first. PFS for subjects without tumor progression at the time of analysis will be censored at their last date of tumor evaluation.
Time to progression (TTP)	Time (days) from start of study treatment until objective tumor progression; TTP does not include deaths.

3 Introduction - amended

Background information

Fibroblast growth factors (FGF) and their corresponding receptor family (FGFR) drive crucial oncogenic signaling pathways including cell proliferation, survival and migration (1)(2). FGFRs are commonly altered in various human tumor diseases, including FGFR1 amplification in non-small cell lung cancer (e.g. sqNSCLC (3)(4)), squamous cell carcinoma of the head and neck (SCCHN (38)), or activating mutations of FGFR3 in bladder cancers (BC (5)(6)(7)). These changes contribute to tumor cell growth, sustained angiogenesis, invasion and metastasis and resistance against other therapies.

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), which contains comprehensive information on the study drug. The IB in its most current version is available in the Study File.

Rationale of the study

The target indications for BAY 1163877 in the expansion phase of this study are sqNSCLC, lung adenocarcinoma (LAC), BC and SCCHN. Preclinical data demonstrate a strong anti-tumor efficacy of BAY 1163877 in all four tumor types as a single agent. In human sqNSCLC, amplification of FGFR1 has been demonstrated in up to 21% of cases (8)(9)(10)(11), and FGFR1 amplification was found in 15 % of SCCHN cases (38) which is usually detected by FISH-based analysis of gene copy number alterations. Recent data from the literature, however, suggest that stratification via this approach may not be of sufficient sensitivity as a considerable number of subjects has been identified with low to intermediate gene copy numbers, rendering these subjects ineligible for targeted therapies with other FGFR inhibitors (12)(13). Analysis of responsive and non-responsive xenograft models revealed a strong correlation with total FGFR1, 2 and 3 mRNA expression levels that will be used as a stratification biomarker in the expansion phase of this trial. Additional genetic information needs to be confirmed as data from the literature (10)(14) and in-house data confirmed a strong influence on tumor response through additional oncogenic mutations (e.g. in K-ras). In BC, activating mutations of FGFR3 have been described in up to 70% of cases (15)(6)(16) and will be used as an additional stratification marker if overall mRNA expression in these subjects is low. This stratification approach allows to minimize the risk for subjects who will potentially not benefit and increase the chance for generating early signs of clinical efficacy. Inhibition of FGFR1 leads to the upregulation of FGF23 in serum (17), which will be used as sensitive pharmacodynamic (PD) biomarker. Inhibition of extracellular signal-regulated kinase (ERK) phosphorylation will be assessed as an additional PD biomarker from tumor tissue.

Preclinical data suggest a good tolerability and efficacy in these subject populations after continuous oral dosing with BAY 1163877. [22]

It was shown that FGFR3 expression is inversely correlated to programmed death-ligand 1 (PD-L1) expression and T cell infiltration in tumor tissue of patients with BC (40). This finding was confirmed in archival biopsy samples collected in study 16443. A similar correlation was detected in patients with sqNSCLC and LAC in study 16443.

It is assumed that a causal relationship between FGFR expression and T cell exclusion leads to low PD-L1 levels and decreased responsiveness towards inhibition of the PD-L1 axis. Potentially, inhibition of FGFR can overcome this interaction and render tumors targetable by the immune system.

Immune responses and the tumor microenvironment are inadequately reflected in preclinical cancer models. We therefore aim to analyze selected immune parameters before and during BAY1163877 treatment in paired biopsies and in serum of biomarker-selected patients. Fresh tumor tissue will be used to assess immune parameters indicating a T cell response against the tumor tissue. This will be done by performing gene expression profiling (nCounter PanCancer Immune Profiling Panel) and immunohistochemistry for CD8+ T cell infiltration and PD-L1 expression on the tumor tissue. Peripheral blood will be used to collect serum to determine cytokine levels (IL-6, IFN-gamma, and other cytokines if needed). Aim of the assessment of peripheral blood is to search for changes in this easily accessible specimen that reflect the immune response in the tumor tissue.

Guidance regarding selected adverse events of special interest is provided in Section 8.4.3. Additional details can be found in the IB.

Benefit-risk assessment

BAY 1163877 is expected to demonstrate clinical benefit as additional treatment for subjects with refractory, locally advanced or metastatic solid tumors.

Taken all preclinical data together, BAY 1163877 has an acceptable safety profile with promising therapeutic efficacy. Subjects will be closely monitored for adverse events by the investigator for any adverse events starting from baseline visit till the end of the study visit to ensure the safety of subjects.

The subjects may not personally benefit from participation in the trial. They are the first to receive BAY 1163877 that may possibly become the standard of care. However, the therapy being tested is new, and the side effects in humans are unknown. Subjects participating in this trial will be seen frequently by qualified health care professional who provide care and closely monitor and evaluate the subject's response to the study medication, in terms of its safety and effectiveness. Since there is often no alternative for subjects with advanced, refractory cancer, the risk–benefit ratio for finding the MTD may therefore be acceptable to the subjects.

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[22] The following section was added by Amendment 7, see section 15.6.2.3

The study shall be discontinued in the event of new findings that indicate that a relevant deterioration of the risk - benefit relationship is probable. On the basis of the data available to date, the conduct of the study is regarded as justifiable.

In summary, this Phase I study of BAY 1163877 for the treatment of refractory, locally advanced or metastatic solid tumors is justifiable without exposing subjects to an undue risk.

4 Study objectives - amended

The primary objectives 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

Secondary objectives include:

- 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.

Exploratory objective:

- To evaluate selected immune parameters.[23]

5 Investigator(s) and other study participants - amended

Sponsor's Medical Expert

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Coordinating Investigator for the Study

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[23] Immune parameters added by Amendment 7, see section 15.6.2.4

[24] The medical expert changed, see Amendment 7, section 15.6.2.5

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file (ISF).

Whenever the term 'the investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature sheet before subject recruitment may start at the respective center. Likewise, all protocol amendments / integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor study file.

The global sponsor of this study is identified on the title page of this protocol.

If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

6 Study design - amended

Design overview

This is a Phase I, first-in-human, open-label, non-randomized, multi-center, 2-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 maximum tolerated dose (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. [25]

[25] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.6

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 a maximum of 50 evaluable subjects with BC and at least 8 subjects with SCCHN treated at MTD.[26]

- *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.[27]

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.[26] 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)[28] 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.[29] The dose needs to be taken under supervision and the time

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[26] Modified by Amendment 6, see section 15.6.2.6

[27] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.6

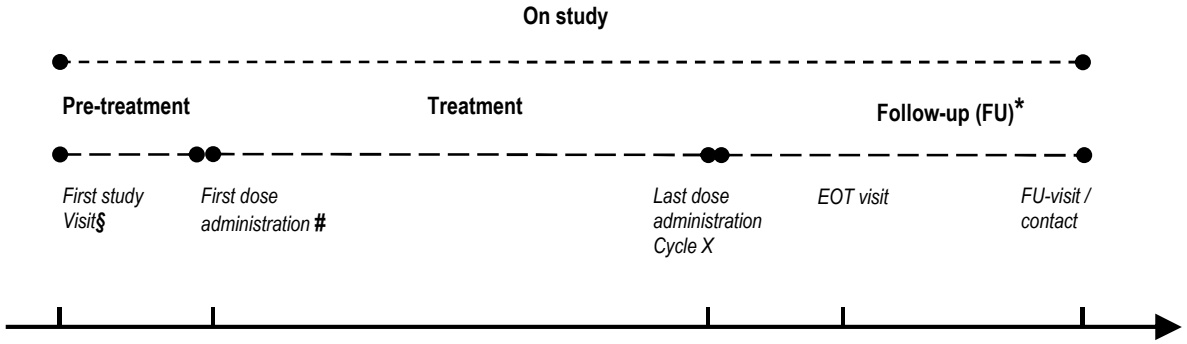
[28] Part 3 was added by Amendment 7, see section 15.6.2.6

[29] PK sampling in Part 3 was added by Amendment 7, see section 15.6.2.6

recorded.

Study periods:

Figure 6-1: Schematic presentation of the treatment design - amended



§ 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,Part 2, or Part 3 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.[30]

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 6-1):

- Pre-treatment
  - Testing for FGFR expression and FGFR mutation (only for subjects recruited for Part 1, Part 2 or Part 3 MTD expansion cohorts)[31]
  - 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 long as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.

[30] Part 3 was added by Amendment 7, see section 15.6.2.6

[31] Part 3 was added by Amendment 7, see section 15.6.2.6

- *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 long 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. [32]

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.[32]

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

The first screening visit is scheduled within 7 days / within 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 (please refer to Section 13.2). The screening period ends just before start of treatment.

The treatment period starts on the day of the first administration of study treatment either 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 End of Treatment (EOT) visit will be performed for all subjects within 0-14 days after

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[32] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.6

administration of the last dose of BAY 1163877. The Follow-up 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) follow-up (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 "drug-free 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").[33] 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 (see Section 8.7).

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), see Section 7.2.1. 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 maximum tolerated dose (MTD)

An adaptive dose escalation design will be used to determine the MTD in study Part 1 (all

[33] Part 3 was added by Amendment 7, see section 15.6.2.6

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 (Section 8.4).

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. In general, the assessment of relationship between adverse events (AEs) and BAY 1163877 will be performed as described in Section 9.5.1.2.3.

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 100mg in increments of 100mg.

- 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 (see details in Section 16.4). 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.

Pharmacokinetics (PK): Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 in the "tablet bridging cohort", and on Cycle 1, Days 1 and 15 in all subjects participating in Part 1 (all comer) and in at least 12 subjects participating in Part 2 (sqNSCLC + LAC + BC + SCCHN). In approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2), the effect of food on the PK of BAY 1163877 will be determined by comparing exposures on Cycle 1 Day -3 (administration after consumption of a high-fat, high-calorie breakfast) and Cycle 1 Day 1 (administration after an overnight fast of at least 8 hours), see Section 8.1. In the MTD expansion cohorts, in approximately 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated formula), serial PK blood samples will be collected on Cycle 1 Day 1 and Day 15. In all

subjects participating in Study Part 3/"Safety cohort", multiple dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day 15.[34]

Plasma concentration of BAY 1163877 will be measured using a validated method.

In approximately 8 subjects enrolled in MTD expansion cohorts (study Part 1 and Part 2), urine will be collected for 24 hours after dosing on Cycle 1, Day 1 (concurrently with plasma PK samples) and analyzed using validated method.

Exploratory monitoring of metabolites may also be performed in pooled plasma samples (most likely at the MTD or the therapeutic dose) and urine samples.

The time points for PK sampling and further details are provided in Section 9.4.2.1.

Safety / tolerability: Drug safety will be monitored and evaluated continuously throughout the study, including a 30-day follow up period (time window +5 days) after administration of the last dose of BAY 1163877.

Safety will be assessed by close monitoring and timely assessment of adverse events (AEs), laboratory parameters (blood tests, urinalysis), vital signs (blood pressure, heart rate), subject's medical condition (physical examination including weight), ophthalmological examination, general well-being and activities of daily life (Eastern Cooperative Oncology Group (ECOG) performance status). [35]

Each subject will be regularly assessed in each cycle for potential AEs and disease related signs and symptoms. The National Cancer Institute's Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE v4.03) will be used to grade toxicities / AEs.

Subject data will be analyzed for evidence of cumulative toxicity with repeated cycles of therapy.

Women of childbearing potential must have a negative pregnancy test performed within 7 days prior to first treatment with BAY 1163877 (i.e. 1 week before Cycle 1, Day 1 or Cycle 1, Day -3, if applicable).

Cardiovascular assessment: Blood pressure (BP) and heart rate (HR) will be measured at screening, frequently on PK profile days in Cycle 1, and once at all other visits during treatment and follow up. The time points for monitoring BP and HR on the days of PK sampling and further details are provided in Section 9.4.1.1.

Assessment of immune priming (Part 3): Selected parameters of immune response will be measured in fresh tumor tissue at baseline and again between Cycle 2, Day 1 and Cycle 2, Day 21; and in peripheral blood at the following timepoints: at baseline; Cycle 1, Day 8; Cycle 2, Day 1; Cycle 2, Day 15; and on the day of the second biopsy.

Fresh tumor tissue will be used to assess immune parameters indicating a T cell response against the tumor tissue. This will be done by performing gene expression profiling

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[34] Part 3 was added by Amendment 7, see section 15.6.2.6

[35] Amended by Amendment 7, see section 15.6.2.6

(nCounter PanCancer Immune Profiling Panel) and immunohistochemistry for CD8+ T cell infiltration and PD-L1 expression on the tumor tissue. Peripheral blood will be used to collect serum to determine cytokine levels (IL-6, IFN-gamma, and other cytokines if needed). Aim of the assessment of peripheral blood is to search for changes in this easily accessible specimen that reflect the immune response in the tumor tissue.[36]

Electrocardiogram (ECG): 12-lead ECG readings will be performed at screening, on Cycle 1, Days -3 and -2 ("tablet bridging cohort" and "food effect assessment", only), on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle, and at the EOT visit. In all Cycles and at the EOT visit, ECG readings will be performed as single readings. The time points for ECG readings and further details are provided in Section 9.5.3.4.

Pharmacodynamic (PD) biomarkers: In an attempt to demonstrate the mechanism of action of BAY 1163877 biomarkers will be studied in tissue samples (for details see Section 9.4.4).

Biomarker analysis in tumor tissue: Biomarker analysis will be done at screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN; Part 3: sqNSCLC + LAC + BC) according to FGFR expression levels / FGFR mutation using either an archival tumor tissue specimen or fresh tumor biopsy material (see Section 7.1.1, inclusion criteria).[37]

Analysis of phospho-extracellular signal-regulated kinase 1/2 levels, (p-ERK1/2) will be done at screening and on Cycle 2, Day 1 for all subjects of study Part 1 and Part 2 who are willing to undergo a biopsy both at screening and on Cycle 2, Day 1.[38] Both biopsies are mandatory for "all comer" subjects included in the MTD expansion cohort of Part 1 (please refer to Section 7.1.1 for details).

Tumor response evaluation: Computed tomography (CT) or magnetic resonance imaging (MRI) of all anatomic regions involved with the disease will be performed at screening (baseline), at the end of Cycle 2 and thereafter every third cycle to assess tumor response using the Response Evaluation Criteria in Solid Tumors, Version 1.1. (RECIST v1.1)(1).

Response evaluation according to RECIST v1.1 can be done up to 5 days after CT / MR scan.

Recommended Phase II dose (RP2D): The dose recommended for Phase II studies with BAY 1163877 will be determined by the investigators and the sponsor (DSMT) at the end of this study (after Part 2) after having reviewed the data from all dose levels evaluated including PK data, overall incidence and severity of AEs, cardiac safety, and amount of MTD.

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[36] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.6

[37] Part 3 was added by Amendment 7, see section 15.6.2.6

[38] 'Study Part 1 and Part 2' added by Amendment 7 for clarification, see section 15.6.2.6

6.1 Primary variable(s)

This is primarily a descriptive safety and tolerability Phase I study. The primary variable for MTD determination will be the incidence of DLTs during the first 21 days of treatment (Cycle 1). The primary study outcome is the MTD being defined as the maximum dose at which the incidence of DLTs during Cycle 1 is below 20%.

Primary PK parameters are provided in Section 9.4.2.2.

6.2 Justification of the design - amended

For study objectives please see Section 4.

The study will be conducted at multiple sites worldwide to ensure recruitment of a sufficient number of subjects with advanced solid organ malignancies. The sites must be specialized in tumor assessment according to RECIST 1.1 and must be well equipped to conduct the efficacy and safety evaluations required by the protocol.

Only subjects for whom in the opinion of the investigator, experimental therapy with BAY 1163877 may be beneficial are allowed to participate. Life expectancy in most of those subjects is expected to be about 3 months. Dosing with BAY 1163877 may continue without evidence of tumor reduction or stable disease as long as, in the judgment of the investigator, some benefit is being derived. The inclusion of a placebo control or blinding of the treatment is considered not applicable for the objectives of this dose-escalation study (identification of MTD / RP2D).

The open-label, non-randomized, dose-escalating design is the standard design to define the safety profile, MTD, PK, PD biomarker and tumor response profile in subjects with advanced malignancies.

Once DLTs are reported, the use of adaptive dose-selection decisions according to pre-specified safety rules based on actual DLT observations is chosen because it permits a better determination of the MTD with reduced sample size, while limiting the number of subjects being treated with toxic doses.

The "all-comers" design in study Part 1 will allow for expedited accrual of subjects and evaluation of safety in subjects with varied solid tumor types (any solid tumors).

Study Part 3 / “Safety cohort” (sqNSCLC + LAC + BC)[39]

Preliminary safety data of patients with advanced cancer treated with BAY 1163877 showed a favorable safety profile (details can be found in the current version of the IB). However, sample size is still limited in selected indications (sqNSCLC, LAC, BC) and additional safety data will be generated in Study Part 3 “Safety cohort”. In parallel, additional efficacy data will be collected and changes of selected immune parameters will be assessed in Part 3.

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[39] The following section was added by Amendment 7, see section 15.6.2.7

It was shown that FGFR3 expression is inversely correlated to programmed death-ligand 1 (PD-L1) expression and T cell infiltration in tumor tissue of patients with BC (40). This finding was confirmed in archival biopsy samples collected in study 16443. A similar correlation was detected in patients with sqNSCLC and LAC in study 16443.

Recently, the PD-1 and PD-L1 inactivating antibodies received accelerated approval by the FDA for patients with BC. It was demonstrated that patients with a low expression of PD-L1 had a smaller chance to respond to atezolizumab treatment.

It is assumed that a causal relationship between FGFR expression and T cell exclusion leads to low PD-L1 levels and decreased responsiveness towards inhibition of the PD-L1 axis. Potentially, inhibition of FGFR can overcome this interaction and render tumors targetable by the immune system.

Immune responses and the tumor microenvironment are inadequately reflected in preclinical cancer models. We therefore aim to analyze selected immune parameters before and during BAY1163877 treatment in paired biopsies and in serum of biomarker-selected cancer patients. Fresh tumor tissue will be used to assess immune parameters indicating a T cell response against the tumor tissue. This will be done by performing gene expression profiling (nCounter PanCancer Immune Profiling Panel) and immunohistochemistry for CD8+ T cell infiltration and PD-L1 expression on the tumor tissue. Peripheral blood will be used to collect serum to determine cytokine levels (IL-6, IFN-gamma, and other cytokines if needed). Aim of the assessment of peripheral blood is to search for changes in this easily accessible specimen that reflect the immune response in the tumor tissue.

6.3 End of study

For each participating EU country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last subject (LPLV) for all centers in the respective country has occurred.

As for this study, the primary outcome will be analyzed at 6 months from last patient first visit (LPFV) or after LPLV, whatever comes first.

The end of the study as a whole will be the date when the clean data base is available.

However, the LPLV date can also be reached based on the last patient stopping study treatment, switching to a roll-over study, or being switched to commercial drug supply with no cost to the patient.

If the trial is stopped but benefits are observed for patients, further treatment options may be discussed and agreed between the investigator, sponsor and the patients.

See also Sections 8.2 and 8.8 for further details on the roll-over study.

7 Study population

Subjects with histologically or cytologically confirmed refractory, locally advanced or metastatic solid tumors are eligible. Subjects should have evaluable or measurable disease.

Subjects' tumors must be refractory to standard treatment, have no standard therapy available or subjects who actively refused cytotoxic chemotherapy which would be regarded standard, and / or if, in the judgment of the investigator, experimental treatment is clinically and ethically acceptable.

7.1 Eligibility

7.1.1 Inclusion criteria

7.1.1.1 Eligibility criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 1, Part 2 and Part 3) - amended[40]

- Ability to understand and willingness to sign the written subject information sheet / informed consent form (SIS / ICF) for FGFR expression / FGFR mutation testing (see Section 13.2). Signed informed consent (IC) has to be obtained before any study specific procedure.
- Subjects with histologically or cytologically confirmed, refractory, locally advanced or metastatic solid tumors (all comer for study Part1; sqNSCLC, LAC, BC or SCCHN for Part 2; sqNSCLC, LAC, or BC for Part 3) who are not candidates for standard therapy. [40]
- Male or female subjects ≥18 years of age
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2
- Life expectancy of at least 3 months
- Existence of archival or fresh tumor biopsy specimen for FGFR expression / FGFR mutation testing.

Besides these basic criteria, any criterion as outlined below under inclusion and exclusion criteria (Sections 7.1.1.2 and 7.1.2) already known to prohibit the patient's participation in the study should be considered.

7.1.1.2 Eligibility criteria for study treatment - amended

Screening for study treatment eligibility must be performed within 7 days / within 28 days prior to the first dose of study drug. Subjects must fulfill all of the following criteria before being included in the treatment phase (i.e, before receiving any dose of BAY 1163877):

- Ability to understand and willingness to sign the written SIS / ICF for study

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[40] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.8

treatment eligibility. Signed IC obtained before any (further) study specific procedure.

- Subjects with histologically or cytologically confirmed, refractory, locally advanced or metastatic solid tumors who are not candidates for standard therapy. Subjects with any type of solid tumors (all comer) will be eligible for dose escalation and dose expansion at MTD in Part 1.

- Subjects enrolled in the MTD expansion cohorts of Study Part 1, Part 2 and Part 3 must present high FGFR expression levels based on archival or fresh tumor biopsy specimen analysis.
Bladder cancer subjects with low overall FGFR expression levels can be included if activating FGFR3 mutations are confirmed.
(only for MTD expansion cohorts of study Part 1 (all comer), Part 2 (sqNSCLC + LAC +BC + SCCHN) and Part 3 (sqNSCLC + LAC + BC)).[41]

- Subjects must have at least one measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. A lesion in a previously irradiated area is eligible and to be considered as measurable disease as long as there is objective evidence of progression of the lesion prior to study enrollment.

- Subjects with resected primary tumors who have documented metastases are eligible.

- Subjects consent to undergo a paired biopsy at screening and on Cycle 2, Day 1
(only for MTD expansion cohorts of study Part 1(all comer))

Note: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy for biomarker (p-ERK1/2) studies is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.[42]

- Subjects consent to undergo paired biopsies at screening and between Cycle 2, Day 1 and Cycle 2, Day 21
(only for Study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC)) [43]

- Male or female subjects ≥18 years of age

- Life expectancy of at least 3 months

- Recovery to National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE v4.03) Grade 0 or 1 level or recovery to baseline preceding the prior treatment from any previous drug / procedure-related toxicity (subjects with persistent alopecia, anemia, and / or hypothyroidism can be included).

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[41] Part 3 was added by Amendment 7, see section 15.6.2.9

[42] Amended by Amendment 7, see section 15.6.2.9

[43] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.9

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2
- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting the study treatment:
  - Absolute neutrophil count (ANC) ≥ 1,500/mm^3
  - Platelet count ≥ 75,000/mm^3
  - Total bilirubin ≤ 1.5 times the upper limit of normal (ULN). Documented Gilbert syndrome is allowed if total bilirubin is mildly elevated (< 6 mg/dL).
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
  - Alkaline phosphatase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
  - Lipase ≤ 5 x ULN
  - Not more than Child-Pugh score B7 hepatic impairment
  - Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 according to the modified diet in renal disease (MDRD) abbreviated formula
- International normalized ratio (INR) ≤ 1.5 x ULN and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN. Subjects being treated with anticoagulant, e.g. warfarin or heparin, will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. Close monitoring of at least weekly evaluations will be performed until INR is stable based on a pre-dose measurement as defined by the local standard of care.
- Subjects with a history of hypertension should be on stable anti-hypertensive medicine for more than 7 days before start of study treatment.
- Women of childbearing potential and men must agree to use adequate contraception before entering the program until at least 8 weeks after the last study drug administration. The investigator or a designated associate is requested to advise the subject on how to achieve an adequate birth control. Adequate contraception is defined in the study as any medically recommended method (or combination of methods) as per standard of care.
- Women of childbearing potential must have a pregnancy test performed a maximum of 7 days before start of study treatment, and a negative result must be documented before start of study treatment.

7.1.2 Exclusion criteria

Subjects are to be excluded from the study if they display any of the following criteria:

7.1.2.1 Exclusion criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 1)

- No archival biopsy available and no consent to obtain tumor biopsy.
- Subject still on anticancer treatment or in the washout period of a previous anticancer treatment (defined as 5 half-lives of the anticancer agent [or 6 weeks for mitomycin C, nitrosureas and monoclonal antibodies]) at the time the fresh biopsy would be obtained if no archival biopsy is available

7.1.2.2 Exclusion criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 2 and Part 3) - amended[44]

- No archival biopsy available and no consent to obtain tumor biopsy.

7.1.2.3 Exclusion criteria - amended

- FGFR testing shows low FGFR expression levels
(only for MTD expansion cohorts of study Part 1 (all comer), Part 2 (sqNSCLC + LAC + SCCHN) and Part 3 (sqNSCLC + LAC))
- No consent for mandatory paired biopsies for biomarker (Part 1) or assessment of immune parameters (Part 3)
(only for MTD expansion cohorts of study Part 1 (all comer) and study Part 3 (sqNSCLC+ LAC + BC)[45]
- FGFR expression / FGFR mutation testing shows low FGFR expression levels and absence of activating mutation in FGFR3 gene
(only for Part 2 and Part 3 (BC))

Medical and surgical history

- Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study except cervical carcinoma in situ, treated basal cell carcinoma or any cancer curatively treated > 3 years prior to start of study treatment
- Previous treatment with anti-FGFR directed therapies (e.g. receptor tyrosine kinase inhibitors or FGFR-specific antibodies)
- Symptomatic metastatic brain or meningeal tumors unless the subject is > 6 months from definitive therapy, has no evidence of tumor growth on an imaging study within 4 weeks prior to start of study treatment and is clinically stable with respect to the tumor at the start of study treatment. Also the subject must not be undergoing acute steroid therapy or taper (chronic steroid therapy is acceptable provided that the dose is stable for

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[44] Part 3 was added by Amendment 715.6.2.11

[45] Part 3 was added by Amendment 7, see section 15.6.2.11

one month prior to and following screening radiographic studies).

- History or current condition of an uncontrolled cardiovascular disease including congestive heart failure (CHF) > NYHA (New York Heart Association) Class 2, unstable angina (symptoms of angina at rest) or new-onset angina (within last 3 months) or myocardial infarction (MI) within past 6 months and cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted)
- History of human immunodeficiency virus (HIV) infection or chronic hepatitis B or C
- Active clinically infections (> CTCAE v4.03 Grade 2)
- Seizure disorder requiring medication
- History of organ allograft
- Evidence or history of bleeding diathesis or coagulopathy
- Any hemorrhage / bleeding event ≥ CTCAE v4.03 Grade 3 within 4 weeks prior to the start of study medication
- Serious, non-healing wound, ulcer or bone fracture
- Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation
- Unresolved toxicity higher than CTCAE v 4.03 Grade 1 (excluding alopecia, anemia and / or hypothyroidism) attributed to any prior therapy / procedure
- Any condition that is unstable or could jeopardize the safety of the subject and their compliance in the study
- Any malabsorption condition
- Pregnant or breast-feeding subjects

Medication, drug use and special behavioral patterns

- Prior treatment with BAY 1163877. Subjects permanently withdrawn from study participation will not be allowed to re-enter the study.
- Concomitant therapies that cannot be discontinued or switched to a different medication prior to study entry that are known to increase serum phosphate levels are not permitted within 4 weeks prior to start of study treatment).
- Anticancer chemotherapy or immunotherapy during the study or within 5-half-lives prior to start of study treatment. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks before starting to receive study treatment or within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies. Acute toxic effects of previous anticancer chemotherapy or immunotherapy have to be normalized completely (excluding alopecia). Anticancer therapy is defined as any agent or combination of agents with clinically proven anti-tumor activity administered by any route with the purpose of affecting the

malignancy, either directly or indirectly, including palliative and therapeutic endpoints.

- Use of strong inhibitors of CYP3A4 and strong inducers of CYP3A4 should have been stopped 2 weeks before start of study treatment (see Section 16.11).
- Radiotherapy to target lesions during study or within 3 weeks of start of study treatment. Palliative radiotherapy is allowed.
- Use of systemic corticosteroids within 2 weeks of start of study treatment above the Cushing threshold
- Autologous bone marrow transplant or stem cell rescue within 4 months of start of study treatment
- Major surgery, open biopsy or significant traumatic injury within 4 weeks of start of study treatment
- Subjects undergoing renal dialysis

Electrocardiogram (ECG), blood pressure, heart rate

- Systolic / diastolic blood pressure ≤ 100/60 mmHg and heart rate ≥ 100/min (measured with the subject in a sitting position for at least 2 minutes).

Physical examination

- Clinically relevant findings in the physical examination

Laboratory examination

- Positive pregnancy test
- Deviations of the screened laboratory parameters from the defined ranges (see inclusion criteria)

Other

- Subjects unable to swallow oral medications
- Close affiliation with the investigational site; e.g. a close relative of the investigator or a dependent person (e.g. employee of or student at the investigational site)
- Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results

7.1.3 Justification of selection criteria

The selection criteria are chosen to ensure that subjects with specific risks for administration of the study drugs and / or subjects with conditions which may have an impact on the aims of the study are excluded.

7.1.4 Justification for gender selection

As this is a Phase 1, dose-escalation trial, no specific gender distribution is necessary.

The envisaged indication for BAY 1163877 is treatment of refractory, locally advanced or

metastatic solid tumors in males and females. The proportion of male and female subjects enrolled in this study depends only on the availability of eligible subjects at the study site.

7.2 Withdrawal of subjects from study

7.2.1 Withdrawal - amended

Subjects will be withdrawn from the study for the following reasons:

- Consent withdrawal
  - At their own request or at the request of their legally acceptable representative
  - At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Substantial non-compliance with study procedures
  - Subject who is off study drug (BAY 1163877) longer than 8 consecutive days in Cycle 1
  - Subjects lost to follow-up
- Violation of in- / exclusion criteria (subject no longer eligible for the study)
  - If the subject develops conditions which would have prevented his / her entry into the study according to the in- / exclusion criteria, he / she must be withdrawn immediately if safety is concerned; in other cases, the investigator will decide whether there is a conflict with the study objectives.
  - The development of a second malignancy that requires a different treatment.
  - Development of any intercurrent illness or situation which may, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a relevant degree.
  - Subjects with a positive urine beta-HCG test confirming pregnancy. Pregnancy will be reported under the same timelines as a serious adverse event.
- Unacceptable toxicity
  - If, in the investigator's opinion, continuation of study would be harmful to the subject's well-being
  - Severe allergic reactions, such as exfoliate erythrodermia, anaphylaxis, or vascular collapse
  - Any other potential adverse reaction deemed sufficiently serious to warrant discontinuation of treatment by the investigator or his designated associate(s).
  - Use of illicit drugs or other substances that may, in the opinion of the investigator or his designated associate(s), have a reasonable chance of contributing to toxicity

or otherwise confound the results.

- Retinal detachment of grade 2 or higher according to CTCAE v4.03 [46]
- AST/ALT > 3xULN with concomitant bilirubin > 2xULN in the absence of another reason for these elevations[46]
- AST/ALT > 8xULN or AST/ALT > 5xULN for > 2 weeks if no other reason is found for these elevations[46]

- Tumor progression
  - Subjects with documented disease progression, unless the investigator (in consultation with the sponsor) deems that continued treatment is appropriate. Patients may continue if they experience clinical benefit as assessed by the investigator, do not exhibit rapid disease progression and have stable performance status. In addition, treatment beyond progression should not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases).[46]
- At specific request of the sponsor

In all cases, the reason for withdrawal must be recorded in the electronic case report form (eCRF) and the subject's medical record.

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".

Any subject removed from the study will remain under medical supervision until discharge or transfer is medically acceptable.

Details for the premature termination of the study as a whole (or components thereof [e.g. centers, dose steps]) are provided in Section 12.

7.2.2 Replacement

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 (see Section 8.7) 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

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[46] Withdrawal criteria were added by Amendment 6, see section 15.6.2.12

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.

7.3 Subject identification

Each subject who signs a consent form for the study will be assigned a unique 9-digit screening number (SNR) in ascending order of recruitment into the study at that center. The first 2 digits will refer to the country, the subsequent 3 digits to the site number, and the following 4 digits will be subject identifiers.

This SNR will be entered into the electronic case record form (eCRF) regardless of whether the subject is actually treated with the study drug (BAY 1163877).

Subjects who are not treated will be considered screening failures. The reason for screening failure should be recorded in the eCRF.

8 Treatment(s)

8.1 Treatments to be administered - amended

Investigational medicinal product (IMP) – test drug

- BAY 1163877 drinking solution (test drug)
- BAY 1163877 tablet (test drug)

Non-investigational product(s) (NIMP)

Not applicable

In study Part 1 / dose escalation + MTD expansion (all comer), twice daily dosing of BAY 1163877 follows the dose-escalation scheme described in Section 6 (Determination of the maximum tolerated dose (MTD)).

Study Part 1 starts with single-dose administration of 50 mg BAY 1163877 on Cycle 1, Day 1. After a “drug-free day” (Cycle 1, Day 2), multiple doses of BAY 1163877 will be given twice daily in an adaptive dose escalation manner, starting at a dose of 100 mg / day (50 mg b.i.d.), with possible dose steps of 100 mg / day. The dose-escalation design proceeds with cohorts of 3 subjects. Cohort expansion, increase or decrease in dose will be decided by the DSMT after consideration of all available safety data of the previous cohort (see Section 6). The dose decision will be guided by model-based dose-response analysis of the DLT rates (see Section 16.4).

In the “tablet bridging cohort”, relative bioavailability of the tablet formulation in comparison to the solution formulation will be assessed by administration of a single dose of the tablet formulation on Cycle 1, Day -3 in at least 3 subjects. Starting with Cycle 1, Day 1, subjects enrolled in this cohort will continue with the solution formulation as described above.

In study Part 1 / MTD expansion (all comer), subjects will receive the MTD of

BAY 1163877 determined at the end of dose escalation.

For the "food effect assessment", subjects will receive one single dose of BAY 1163877 on Cycle 1, Day -3 immediately (within 5 min) after consumption of a high-fat, high-calorie breakfast, and a second single dose BAY 1163877 on Cycle 1, Day 1 after an overnight fast of at least 8 hours. Further details are provided in Section 8.4.2.2.1.

In study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN), subjects will be treated with the MTD of BAY 1163877 determined in study Part 1.

In study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC), subjects will be treated with the MTD of BAY 1163877 determined in study Part 1. [47]

8.2 Identity of study treatment

The details of the two formulations of BAY 1163877 planned to be used in this study are given in Table 8-1 (solution) and Table 8-2 (tablet).

Table 8-1: Identity of test drug (IMP): BAY 1163877 solution formulation

Generic name / brand name / INN	Not applicable
Substance code number(s)	BAY 1163877 as BAY 1213802
Material / (formulation)	BAY1163877 HCl H2O SOL 1% 11 mL ORAL
Galenical form / formulation / vehicle and reconstitution, if applicable	Ready-to use solution for oral application
Composition	Active ingredients: BAY 1163877 as hydrochloride Other ingredients: Hydroxypropylbetadex (solubilizer) Sucralose (sweetener) Sodium benzoate (preservative) Hydrochloric acid (pH-adjustment agent) Sodium hydroxide (pH-adjustment agent) Purified water (solvent)
Strength (amount of drug per unit) or concentration	1% (10 mg of BAY 1163877 per 1 mL solution)
Type of packaging and content	Amber glass bottle with a withdrawable volume of 11 mL corresponding to 110 mg BAY 1163877
Marketing Authorization Holder if applicable	Not applicable

[47] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.13

Table 8-2: Identity of test drug (IMP): BAY 1163877 tablet formulation

Generic name / brand name / INN	Not applicable
Substance code number(s)	BAY 1163877 as BAY 1213802
Material / (formulation)	BAY 1163877 HCL TAB 50.0 mg 363 COAT BAY 1163877 HCL TAB 200.0 mg 364 COAT
Galenical form / formulation / vehicle and reconstitution, if applicable	IR (immediate release) tablets
Composition	Active ingredients: BAY 1163877 as hydrochloride Other ingredients: Cellulose microcrystalline (filler) Lactose monohydrate (filler) Crospovidone (disintegrant) Copovidone (binder) Magnesium stearate (lubricant) Silica colloidal anhydrous (glidant) Lacquer red (coating material)* * (contains hypromellose, macrogol, titanium dioxide,ferric oxide red)
Strength (amount of drug per unit) or concentration	50 mg BAY 1163877 per tablet 200 mg BAY 1163877 per tablet
Type of packaging and content	HDPE bottles with screw cap closure or blisters of Foil 25/45/60 µm oPA/Al/PP (4320 / 0257) sealed to Foil 20 µm Al sealable to PP (4345 / 0202)
Marketing Authorization Holder if applicable	Not applicable

Labeling: Study medication will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request. Storage conditions are provided on the label.

For all study drugs, a system of numbering in accordance with all requirements of good manufacturing practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance (QA) group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor study file.

To reorder clinical drug supplies at least 2 weeks advance notice is required. The site should inform the responsible person for the drug reorder. Contact details of the responsible person are provided on the study team list. The responsible person will notify the site when the order for drug has been placed.

All investigational drugs used during the trial will be stored at the site in accordance with instructions given by the clinical supplies delivering department, and will be inaccessible to unauthorized personnel.

Study medication needs to be stored according to the label text. For special storage conditions see investigator site file (ISF) and trial master file (TMF).

In case patients are transferred to a roll-over study (ROS), drug formulation and / or dosage might change compared to this study depending on the course of the clinical development.

8.3 Treatment assignment

After completion of the screening examinations, subjects who meet the entry criteria will be placed in the current cohort at the specified dose level. A random list is not necessary because this is a non-randomized open label clinical trial. All subjects will be assigned a unique screening number (SNR), whether or not they are treated after the first signed informed consent. For subject identification, see Section 7.3.

8.4 Dosage and administration

Please refer to Sections 8.1 and 8.2 for the dose, route of administration, formulation and duration of treatment.

8.4.1 Estimation of safe starting dose

Study Part 1 / dose escalation (all comer)

The first cohort is treated at a starting dose of 100 mg / day of BAY 1163877 (50 mg b.i.d.) which is considered to be safe based on extrapolation from animal toxicological data.

The dose level for each dose-escalation step will be defined primarily based on the results with regard to safety, tolerability, and, if available, PK of the previous dose steps. For this reason, an evaluation will be conducted after each dose step and the decision for the next step will be made by the study team. If necessary, the dose of the next step will be adopted. Details for the dose-escalating steps are given in Section 6 (Determination of the maximum tolerated dose (MTD)).

8.4.2 Selection and timing of dose for each subject - amended

Details for the dose-escalating steps in study Part 1 / dose escalation + MTD expansion cohort (all comer) as well as extent and duration of drug exposure of the individual subject are given in Section 6 (Determination of the maximum tolerated dose (MTD)). Safety monitoring will occur by teleconferences with participation of the investigators and representatives of the sponsor on a regular basis (DSMT). Dose escalation for subsequent cohorts will only be considered after all subjects from the previous cohort have completed the first cycle or early discontinued.

Extent and duration of drug exposure of the individual subject in study Part 2 / dose expansion (sqNSCLC + LAC + BC + SCCHN) and study Part 3 / dose expansion “Safety

cohort" (sqNSCLC + LAC + BC) are given in Section 6.[48]

8.4.2.1 Dosing schedule - amended

BAY 1163877 will be given in cycles. Each cycle lasts 21 days. There will be no break between treatment cycles.

Subjects will receive either the solution (IMP 1) or the tablet (IMP 2) formulation of BAY 1163877, except for subjects in the "tablet bridging cohort" who will receive both a single dose using the tablet formulation and multiple doses using the solution formulation.

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

Cycle 1 Day -3 ("tablet bridging cohort" only):	Single-dose administration of BAY 1163877 tablet formulation on Cycle 1, Day -3; thereafter continuation with solution formulation starting on Cycle 1, Day 1 (see dosing schedule below)
Cycle 1:	Single-dose administration of BAY 1163877 on Cycle 1, Day 1 (in the morning) No administration of BAY 1163877 on Cycle 1, Day 2 ("drug-free day") Twice daily administration of BAY 1163877 on Days 3-21
Cycle 2 and subsequent cycles:	Twice daily administration of BAY 1163877 on Days 1-21.

Study Part 2 / dose expansion (sqNSCLC + LAC + BC + SCCHN):

- Subjects participating in PK assessments will follow the dosing regimen specified for study Part 1.
- Subjects without PK assessment will receive BAY 1163877 twice daily from Cycle 1, Day 1 ongoing.

Study Part 1 (MTD expansion cohort) or Study Part 2 / "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). BAY 1163877 will not be administered on Cycle 1, Day -2 and Day -1, in the evening of Cycle 1, Day 1 and on Cycle 1, Day 2.

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

- Subjects will receive BAY 1163877 twice daily from Cycle 1, Day 1 ongoing.[49]

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[48] Part 3 added by Amendment 7, see section 15.6.2.14

[49] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.15

Evidence of tumor progression, unacceptable toxicity, consent withdrawal or subject's withdrawal from the study at the discretion of the Investigator may lead to termination of treatment (see Section 7.2.1).

8.4.2.2 Mode of administration

BAY 1163877 will be administered per os (p.o.). Subjects participating in "food effect assessment" will receive a single dose after consumption of high-fat, high-calorie meal (Cycle 1, Day -3) and a single dose after an overnight fast of at least 8 hours (Cycle 1, Day 1) see Section 8.4.2.2.1.

The ready-to-use solution will be administered directly and undiluted via disposable syringe into the mouth of the subject. Immediately after administration, the subject has to drink a glass of water (approximately 200 mL / 7 ounces).

BAY 1163877 tablets should be taken with a glass of water (approximately 200 mL / 7 ounces). Tablets should be swallowed intact and not chewed.

Subjects should not take additional doses of BAY 1163877 to compensate for a missed dose.

8.4.2.2.1 Food effect assessment

To assess the effect of food on the PK of BAY 1163877, a single dose of BAY 1163877 will be administered immediately (within 5 minutes) after consumption of a high-fat, high-calorie breakfast on Cycle 1, Day -3 followed by PK profiling in subjects participating in the MTD expansion cohorts of study Part 1 and Part 2.

Examples of high-fat, high-calorie breakfast:

A) 50 grams of smoked cooked ham, 30 grams of chicken liver sausage, 50 grams of rye bread, 7 ounces (210 mL) whole milk, 40 grams of butter, 30 grams of butter cheese and 17 Crispbread Wasa Mjölk

B) 2 eggs (fried), 2 strips of bacon, 2 slices of bread toast, 8 ounces (240 mL) whole milk and 3 teaspoons of butter (for frying and for toast)

High-fat, high-calorie breakfast may be adapted depending on the country while maintaining similar fat and calorie content (approximately 50 % fat and 800 to 1000 calories). Breakfast should be consumed within 25 minutes. No snack is permitted for 4 hours after study drug administration.
BAY 1163877 will not be administered on Cycle 1, Day -2 and Day -1.
A single dose of BAY 1163877 will be administered on Cycle 1, Day 1 after an overnight fast of at least 8 hours (water is allowed *ad libitum*) followed by PK profiling. No food or snack is permitted for 4 hours after drug administration, but water is allowed 1 hour after dosing.

Study drug will not be administered in the evening of Cycle 1, Day 1 and on Cycle 1, Day 2 ("drug-free day").
Starting with Cycle 1, Day 3, BAY 1163877 will be taken twice daily.

8.4.2.3 Treatment duration

BAY 1163877 will be administered on a continuous schedule in at least one 21-day Cycle with no break between cycles until progression or as long as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.

For subjects in the "tablet bridging cohort" and "food effect assessment", treatment starts on Cycle 1, Day -3.

For all other subjects, treatment starts on Cycle 1, Day 1.

Further details on dosing schedule are provided in Section 8.4.2.1.

8.4.3 Dose modification and delays - amended

Doses of study drug (BAY 1163877) may be delayed or reduced in case of clinically significant hematologic and other toxicities that are possibly, probably or definitely related to study drug therapy. Toxicities will be graded using the CTCAE v 4.03 (see Section 16.5).

No intra-subject dose escalation will be permitted. However, the dose can be reduced or delayed for an individual subject based on toxicities that are related to study drug.

If a subject experiences a DLT during Cycle 1, the next dose of BAY 1163877 can be delayed for up to 21 days, but only in cases Grade 3 non-hematological toxicities persist no longer than 7 days.

All subjects who are re-treated following a DLT should undergo dose reduction (see Table 8-3).

If the toxicity resolves to ≤ Grade 1, the next dosing of BAY 1163877 at 1 dose level below the current dose (see Table 6-3) can be considered, provided that this dose level has been evaluated during the dose escalation part of the study. Detailed dose adjustments for hematological toxicities are described in Table 8-4. If the subject was dosed at the starting dose level, the subject should be removed from the study. If the toxicity fails to resolve to ≤ Grade 1within 21 days after the planned treatment date, the subject will be removed from the study. Subjects who experience a Grade 4 non-hematological toxicity will be removed from the study.

Drug-related adverse events of ≥ Grade 3

For ≥ Grade 3 adverse event regarded as related to study drug, the next dosing of BAY 1163877 can be delayed for up to 21 days. If the toxicity fails to resolve to ≤ Grade 1 within 21 days after the scheduled dosing date, the subject will be removed from the study. If the toxicity resolves to ≤ Grade 1, the next dosing of BAY 1163877 at 1 dose level below the current dose (see Table 8-5) can be considered, provided that this dose level has been evaluated during the dose escalation part of the study. Dose adjustments for toxicities are detailed in Table 8-3.

If the re-treatment reproduces the same toxicity grade, the next dosing of BAY 1163877 can be delayed for up to 21 days until the toxicity has resolved to ≤ Grade 1. Re-treatment is possible at 1 dose level below the previous dose.

Subjects who experience a Grade 4 non-hematological toxicity will be removed from the study. If more than 2 dose reductions are required, treatment will be permanently discontinued.

Table 8-3: Scheme for dose-level reduction of BAY 1163877 in subjects with solid tumors

Dose level	Action
-1	1 dose below level of DLT occurrence[a]
-2	2 doses below level of DLT occurence[a]
-3	Discontinue study drug permanently

a alternatively, treatment can be continued at an interim dose level with at least 3 subjects evaluated

Table 8-4: Hematological criteria for dose delay and dose modification

Grade[a]	ANC (10^9/L)	Platelets (10^9/L)	Dose delay	Dose modification
1 - 2	≥1.0	≥50	Treat as scheduled	No change
3	<1.0 - 0.5	<50 - 25	Delay[b] until ≤ Grade 1	Decrease 1 dose level[c]
4	<0.5	<25	Delay[b] until ≤ Grade 1	Decrease 1 dose level[c]

a Applies to all kinds of hematological toxicities; ANC and platelet count displayed as examples.
b If no recovery after 21 days delay, treatment will be permanently discontinued.
c Dose will not be re-escalated to original dose level after reduction for toxicity. If more than 2 dose reductions are required, treatment will be discontinued.

Table 8-5: Non-hematological criteria for dose delay and dose modification

Grade[a]	Dose delay	Dose modification
1 – 2	Treat as scheduled	No change
3	Delay[b] until ≤ Grade 1	Decrease 1 dose level[c]
4	Discontinue study drug permanently	Discontinue study drug permanently

a Excludes alopecia. A maximum duration of 48 hours of Grade 3 nausea or vomiting will be allowed and not be considered DLT.
b If no recovery after 21 days delay, treatment will be permanently discontinued.
c Dose will not be re-escalated after dose reduction for toxicity. If more than 2 dose reductions are required, treatment will be permanently discontinued.

Liver toxicity

Dose modifications of BAY 1163877 for liver toxicity are presented in Table 8-6. Liver toxicity refers to ALT and / or AST and / or bilirubin increases and / or hepatic failure considered possibly related to BAY 1163877, and graded according to CTCAE v4.03.

Table 8-6: Dose modifications of BAY 1163877 for liver toxicity - amended

Toxicity	Modification schedule
Grade 1-2	No modifications. Treat as scheduled and check AST, ALT and bilirubin weekly for at least 4 weeks.
Grade 3	Hold BAY 1163877 until recovery to ≤ grade 2 or baseline, then reduce 1 dose level and check AST, ALT and bilirubin weekly for at least 4 weeks.[a]
- 1st reappearance	Hold BAY 1163877 until recovery to ≤ grade 2 or baseline, then reduce 1 additional dose level and check AST, ALT and bilirubin weekly for at least 4 weeks[a].
- 2nd reappearance	Withdraw subject from the study treatment.[b]
Grade 3 with ALT or AST > 8x ULN and a concomitant rise in bilirubin (of any degree compared to previous bilirubin level) or hepatic failure (of any degree)	In case of a negative risk-benefit assessment, consider permanent discontinuation at the first occurrence[b,c] OR Hold BAY 1163877 until recovery to ≤ grade 2 or baseline, then reduce 1 dose level and check AST, ALT and bilirubin weekly for at least 4 weeks[a].
-1st reappearance	Withdraw subject from study treatment.[b]
Grade 4 [b]	Withdraw subject from study treatment.[b]

a Dose will not be re-escalated after dose reduction for toxicity[50]
b In case of discontinuation, check AST, ALT, and bilirubin weekly until recovery to baseline or stabilization.
c Subjects with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and / or AST.

Patients with AST/ALT > 3xULN with concomitant bilirubin > 2xULN in the absence of another reason for these elevations have to permanently discontinue study drug. Permanent discontinuation also applies to patients with AST/ALT > 8xULN or AST/ALT > 5xULN for > 2 weeks if no other reason is found for these elevations.[50]

Increased Ca x PO4[51]

Dose modifications of BAY 1163877 for . Ca x PO4 ≥ 70 mg²/dL² considered possibly related to BAY 1163877 are presented in Table 8-7.

[50] Liver toxicity criteria amended by Amendment 6, see section 15.6.2.16

[51] Section amended by Amendment 6, see section 15.6.2.16

Table 8-7: Dose modifications of BAY 1163877 for Increased Ca x PO4 - amended

Toxicity	Modification schedule
Ca x PO4 (≥ 70 mg²/dL²)	Hold BAY 1163877, treat with phosphate chelators and check twice weekly until recovery, to Ca x PO4 < 70 mg²/dL². Resume same dose level, continue phosphate chelators and check weekly for at least 4 weeks.
- 1st reappearance	Hold BAY 1163877, treat with phosphate chelators and check twice weekly until recovery to Ca x PO4 < 70 mg²/dL², then reduce 1 dose level, continue phosphate chelator and check weekly for at least 4 weeks.
- 2nd reappearance	Hold BAY 1163877 and check twice weekly until recovery to Ca x PO4 < 70 mg²/dL², then reduce 1 additional dose level, continue phosphate chelators and check weekly for at least 4 weeks.
- 3rd reappearance	Withdraw subject from study treatment.

In patients with hyperphosphatemia (Ca x PO4 ≥ 70 mg²/dL²), the serum phosphate and calcium levels have to be checked twice weekly until resolution (Ca x PO4 < 70 mg²/dL²).

In patients with hypocalcemia, an additional 12-lead ECG has to be obtained on the day of detection of hypocalcemia.

Retinal detachment

Patients that experience retinal detachment of grade 2 or higher according to CTCAE v4.03 have to be permanently discontinued from study treatment.

8.4.4 Dose-limiting toxicity (DLT)

Adverse events which qualify as DLTs are causally related to study drug (while in turn not all related AEs are regarded as DLT). Dose-limiting toxicity will be defined as any of the following occurring during Cycle 1 of a dose level and regarded by the investigators and / or sponsor to be related to BAY 1163877. The CTCAE v 4.03 will be used to assess toxicities / adverse events (see Section 16.5).

Hematological

- Absolute neutrophil count (ANC) < 500/mm^3 for more than 7 days
- Febrile neutropenia (a disorder characterized by an ANC < 1,000/mm^3 and single temperature ≥ 38.3°C or sustained temperature of ≥ 38.0 °C for more than 1 hour)
- Platelets < 25,000/mm^3
- Grade 3 hemorrhage associated with thrombocytopenia of ≥ Grade 3

Non-hematological

- Non-hematologic Grade 3 or Grade 4 toxicity (nausea and vomiting only if refractory to anti-emetics; excluding alopecia). A maximum duration of 48 hours of Grade 3 nausea or vomiting will be allowed and not be considered DLT.

- Serum calcium (albumin-corrected) x phosphate product > 70 mg^2/dL^2 ($5.6\ mmol^2/L^2$) despite the use of phosphate binders

Miscellaneous

In case an unexpected drug-related toxicity is seen more frequently, this toxicity may be declared a DLT for the remainder of the study after thorough consultation between the investigator and the sponsor.

Any toxicity thought to be related to BAY 1163877 that, at the discretion of the investigator, or his designated associate(s), is thought to warrant withholding the drug. Such toxicities might be Grade-1 or Grade-2 toxicities which interfere with the activities of daily life (e.g. long-lasting fatigue, or anorexia), making a dose reduction necessary in order to ensure the subject's compliance.

For certain toxicities such as laboratory assessments without a clear clinical correlation (e.g. lipase increase without signs of a clinical pancreatitis), a discussion between the investigator and the sponsor may take place if that adverse event should be assessed as DLT necessitating dose reduction.

8.5 Blinding

The study is performed in a non-blinded design because this is considered adequate to meet the study objectives.

8.6 Drug logistics and accountability

Study medication will be stored at the investigational site in accordance with good clinical practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate / contract research organization (CRO)), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the Sponsor study file; the site-relevant elements, of this information will be available in the ISF. The responsible site personnel will confirm receipt of study drug in writing and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

8.7 Treatment compliance

Treatment compliance

The first administration of study medication (BAY 1163877) will be done with a member of the site team. This person will ascertain and document that the subject receives the treatment as planned.

On the following days the subject will self-administer (or a caregiver will administer) BAY 1163877 after he / she has been informed about the correct dosing schedule.

Plasma / serum concentrations will give additional information about the subjects' treatment compliance.

At home, subjects will document the intake of study drug (date and time of dosing) as well as the administered dose on a compliance sheet / paper diary (source document to verify treatment compliance), see Section 9.6.1.

The packages of study medication have to be brought back to the trial site for an additional control.

Compliance will be evaluated by the investigational site based on drug accountability.

The information recorded in the paper diary will be transferred into the eCRF taking into account each dose interruption and / or any individual changes in dosing.

A compliance of at least 80% is required, meaning documented intake of at least 80% of the planned study medication (80 % = 32 doses or 16 days in Cycle 1 with PK assessment [Part 1 and Part 2 only] and 34 doses or 17 days in ≥ Cycles 2 and in Cycle 1 without PK assessment [including Part 3]). [52]

Drug accountability

To have complete control over the distribution and use of the study medication, the drug accountability must be performed before new medication is handed out to the subject.

8.8 Post-study therapy

Further treatment at the end of the study will be at the discretion of the investigator.

At the conclusion of the study, patients who demonstrate clinical benefit may be eligible to continue to receive study drug. They may receive further treatment, assessments and/or be followed either via a roll-over study - subject to approval by the competent health authority and ethics committee - or through any other mechanism in accordance with local legal and compliance rules. This applies to patients on study treatment and in follow-up.

In the event a roll-over study is established, the present study will end when all patients have transitioned into the roll-over study or discontinued from this study for another reason (e.g. consent withdrawn, lost to follow-up, death). Until the transition to the roll-

[52] Modified by Amendment 7, see Section 15.6.2.17

over study, patients will continue to follow all the procedures and visits required in the current version of the protocol.

8.9 Prior and concomitant therapy

For prior therapy, see Section 7.1.2 (Exclusion criteria "Medication, drug use and special behavioral patterns").

Medication other than the investigational product must not be taken during the study without consulting the investigator.

All therapies that are considered necessary for the subject's welfare and that are not expected to interfere with the evaluation of the study drug may be given at the discretion of the investigator.

Disease-specific anti-neoplastic therapies, including kinase inhibitors, chemotherapy, radiation therapy, or surgical intervention, are not allowed during study treatment.

All concomitant medications (including start / stop dates, total daily dose, and indication) must be recorded in the subject's source documentation and in the eCRF. Concomitant use of contrast media needs not to be recorded unless the subjects experiences and AE and there is a reasonable possibility that the event might have been caused by exposure to contrast media.

8.9.1 Drug-drug interactions relevant for BAY 1163877

Oxidative metabolism of BAY 1163877 is mainly catalyzed by CYP3A4 and CYP1A1 and to a lesser extent by CYP2C9. Therefore, drugs and herbal preparations that are strong inhibitors and inducers of CYP3A4 are not permitted during the study. Currently, there are no known approved drugs or herbal preparations that are strong CYP1A1 inhibitors or inducers. However, it should be noted that CYP1A1 is induced in smokers. **The subjects who are current smokers and those with recent history of smoking may have lower plasma concentrations of BAY 1163877.**

Initial *in vitro* study results with BAY 1163877 indicate minor mechanism-based (irreversible) inhibition potential towards CYP 3A4. Since several commonly used drugs are metabolized by CYP 3A4, subjects should be proactively closely monitored for side effects of these comedications due to potentially increased systemic exposure.

In general, subjects should be closely monitored for side effects of all concomitant medications regardless of elimination pathway, especially those with narrow therapeutic index. If possible, narrow therapeutic index drugs that are CYP3A4 substrates should be avoided (see Section 16.11).

No data are available to evaluate the interaction between BAY 1163877 and radiation.

8.9.2 Prohibited concomitant therapy

Concomitant therapy with the following medication is NOT allowed:

- Anticancer chemotherapy or immunotherapy during the study or within 5-half-lives prior to start of study treatment. Antibody treatment should not be given within 6

weeks before starting to receive study treatment. Acute toxic effects of previous anticancer chemotherapy or immunotherapy have to be normalized completely (excluding alopecia, anemia and / or hypothyroidism). Anticancer therapy is defined as any agent or combination of agents with clinically proven anti-tumor activity administered by any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints.

- Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks before starting to receive study treatment or within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies in case of performed biopsy procedure
- Bone marrow transplant or stem cell rescue.
- Investigational anti-tumor agents or anti-neoplastic chemo / hormonal / immunotherapy.
- Radiotherapy to target lesions (palliative radiotherapy is allowed)
- CYP3A4 inhibitors and inducers: BAY 1163877 is mainly metabolized by CYP3A4 and CYP1A1 and to a lesser extent by CYP2C9. Therefore, concomitant use of strong inhibitors of CYP3A4 and strong inducers of CYP3A4 are not permitted for 2 weeks prior to start of study treatment or during the study. Concomitant use of moderate and weak CYP3A4 inducers should be avoided as clinically significant decrease in plasma concentrations of BAY 1163877 cannot be ruled out. Strong CYP3A4 inhibitors and inducers are shown in Section 16.11.
- Concomitant use of herbal preparations containing CYP3A4 inducers (e.g. St John's Wort) are not permitted during the study.
- Grapefruit and grapefruit juice (CYP3A4 inhibitor) consumption is not permitted during the study.
- If possible, narrow therapeutic index drugs that are CYP3A4 substrates (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) should be avoided
- Fluconazole is considered a moderate to strong inhibitor of CYP 2C9 and should be avoided, if possible.
- Therapies that are known to increase serum calcium and / or phosphate levels, especially calcium, phosphate, vitamin D, parathyroid hormone (parathormone).

Therapeutic monitoring should be performed consistent with the local clinical standard of care following dose modification of the investigational agent. In general, subjects should be closely monitored for side effects of all concomitant medications regardless of path of elimination.

8.9.3 Permitted concomitant therapy - amended

- Subjects may receive supportive care for any underlying illness, including dexamethasone, G-CSF and other hematopoietic growth factors to treat acute toxicities,

such as febrile neutropenia, when clinically indicated or at the investigator's discretion.

- Additional concomitant medications such as low dose heparin, gonadotropin releasing hormone agonist or antagonist, antihistamines and intravenous fluid supply are permitted, if clinically indicated
- In view of the maximum dose of 800 mg b.i.d., a risk for clinically relevant drug interaction due to inhibition of BCRP and/or P-gp in the intestine for drugs with a low bioavailability limited by P-gp and BCRP cannot be ruled out. However, based on the maximum achievable plasma BAY 1163877 concentration, risk of clinically relevant drug interaction due to systemic inhibition of BCRP and P-gp is regarded as low.[53]
- Subjects taking narrow therapeutic index medications should be monitored proactively.
- Antiemetic therapy is allowed.
- Treatment with "non-conventional therapies" (such as acupuncture), and vitamin / mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the investigator (to be documented in the source notes and in the eCRF).

9 Procedures and variables

9.1 Schedule of procedures

Time deviations from the given time points will be documented as protocol deviations, if applicable. Respective time windows for visits are specified in the flow chart (see Section 16.1).

9.1.1 Tabulated overview

See study flow charts in Section 16.1.

9.1.2 Timing of assessment

If not stated otherwise, the measures listed in the following sections will be performed by or under the supervision of an investigator.

The same imaging or measuring method must be used for all tests required at baseline (screening) and follow-up.

[53] Added by Amendment 7

9.1.2.1 Pre-treatment

9.1.2.1.1 FGFR expression / FGFR mutation testing (MTD expansion cohorts only) - amended

A separate subject information sheet / informed consent form (SIS / ICF) for FGFR expression / FGFR mutation testing must be signed by all subjects recruited for study Part 1, Part 2 or Part 3 MTD expansion cohort (see Section 13.2).[54]

The following activities / examinations will be performed prior to FGFR expression / FGFR mutation testing:

- Signed informed consent for FGFR expression / FGFR mutation testing
- Inclusion criteria limited to FGFR expression / FGFR mutation testing (see Section 7.1.1.1)
- ECOG performance status assessment
- Demographic data
- Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report
- Complete medical /oncological history, TNM classification (see Section 9.2.3)
- Obtain archival tumor tissue sample for FGFR expression / FGFR mutation testing

  Only, if no archival tumor tissue sample is available which has been handled and processed as described in the lab manual: Perform a biopsy to obtain fresh tumor material

- Toxicity / AE assessment and recording only in case an invasive procedure will be performed to obtain tumor material after subjects´ informed consent

All subjects enrolled into the study will be listed on a subject enrollment log provided by the sponsor's representatives.

9.1.2.1.2 Screening - amended

Pre-study examinations will be performed within 7 days / within 28 days before first administration of BAY 1163877 (i.e. before Cycle 1, Day 1). Due to the fact that not all subjects may fulfill the inclusion / exclusion criteria, a higher number of subjects, than needed to be valid for the evaluation of the study, will be asked to participate in the pre-study (screening) examination. As soon as fulfillment of all criteria is confirmed, the subject is included into the trial. In case all subjects are equally qualified, decision will be made by the sponsor or sponsor representative casting lots.

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[54] Part 3 added by Amendment 7, see section 15.6.2.19

Study specific required screening examinations will only be performed after having received the subject's written IC for study treatment eligibility. The subject information sheet / informed consent form (SIS / ICF) for study treatment eligibility must be signed by all subjects including those subjects presenting FGFR expression / FGFR mutation who have signed the SIS / ICF for FGFR expression / FGFR mutation testing before (see Section 9.1.2.1.1)

The following examinations will be performed prior to the first study drug administration:

Within 28 Days Prior to First Dose of BAY 1163877

- Signed informed consent for study treatment eligibility (within 28 days or earlier), see Section 13.2.
- Inclusion / exclusion criteria
- Demographic data (already collected for subjects of Part 1, Part 2 or Part 3 MTD expansion cohorts, see Section 9.1.2.1.1) [55]
- Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report (already done for subjects of Part 1, Part 2 MTD expansion cohorts or Part 3, see Section 9.1.2.1.1)
- Complete medical / oncological history, TNM classification (see Section 9.2.3) (already done for subjects of Part 1, Part 2 or Part 3 MTD expansion cohorts, see Section 9.1.2.1.1)
- Concomitant diseases and NYHA grading
- Review of baseline toxicities
- Baseline characteristics (smoking habits / history, alcohol consumption)
- Previous and concomitant treatment (medication history up to 4 months prior to start of study treatment, see Section 7.1.2)
- Physical examination with complete review of body systems (see Section 9.5.3.1)
- ECOG performance status assessment (also for subjects of Part 1, Part 2 or Part 3 MTD expansion cohorts, see Section 9.1.2.1.1)
- Single 12-lead ECG reading (see Section 9.5.3.4)
- Send subject to consultant ophthalmologist for ophthalmological examination (see Section 9.5.3.2). New onset of cataract or other abnormalities affecting lens or cornea lead to the exclusion of the subject.
- CT scans of the chest, abdomen and pelvis; CT scans of other metastatic lesions as applicable or MRI and documentation of lesion(s) according to RECIST, v1.1. CT/MRI

[55] Part 3 added here and in the following by Amendment 7, see section 15.6.2.20

scans prior screening can be used for documentation according to RECIST, v1.1, if scans were done the latest 28 days prior to first dose of BAY 1163877 (see Section 9.3.1)

- Virology tests, for details see Table 16-4
- Obtain pre-treatment biopsy:
  - optional for subjects in the dose escalation cohorts of study Part 1 (all comer)
  - mandatory for all subjects in the MTD expansion cohort of Part 1 (all comer).
  - optional for subjects in the MTD expansion cohort of Part 2 (sqNSCLC + LAC + BC + SCCHN)
  - mandatory for all subjects in the study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC)[56]
  - Note 1: A biopsy is mandatory for all subjects in the MTD expansion cohort of Part 1, Part 2 and Part 3 for whom no archival biopsy is available for FGFR expression / FGFR mutation testing. Additional biopsy is not requested if a biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit (see Section 9.1.2.1.1). [57]
  - Note 2: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy for biomarker (p-ERK1/2) studies is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.[58]

Within 7 Days Prior to First Dose of BAY 1163877

- Update of inclusion / exclusion criteria
- Review of baseline toxicities
- Update of concomitant therapy
- Body weight and height, calculation of BMI
- Vital signs (body temperature, respiration rate, blood pressure, heart rate)
- Blood and urine collection for safety laboratory tests. In case of abnormal results caused by intercurrent diseases, short-term treatable conditions or other temporary health disorders, the investigator may decide to repeat the respective screening parameter(s). As a rule, up to 2 repetitions are acceptable, for details see Table 16-4
- *Only for females of childbearing potential:* Urine pregnancy test (the negative

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[56] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.20

[57] Part 3 was added by Amendment 7, see section 15.6.2.20

[58] Amended for clarification by Amendment 7, see section 15.6.2.20

result must be documented before start of study drug treatment)

- Calculation of eGFR (see Section 16.9)
- Documentation of lesion(s) according to RECIST v1.1
- Adverse events before start of treatment (results of physical examination)
- *Only for subjects in Part 3:* peripheral blood sample collection for determination of cytokine levels in serum. [59]

9.1.2.2 Randomization

Not applicable (see Section 8.3).

9.1.2.3 Treatment - amended

For subjects in the "tablet bridging cohort" and "food effect assessment", the treatment phase starts on Cycle 1, Day -3, followed by Cycle 1 (21 days) and a variable number of subsequent Cycles (each of 21 days duration) with no break between Cycles.

For all other subjects, the treatment phase comprises Cycle 1 (21 days) and a variable number of subsequent Cycles (each of 21 days duration) with no break between Cycles.

There will be both visits and possible overnight stays at the study site.

Patients with an estimated GFR in the range 30 mL/ min to 60 mL/min should be carefully monitored for signs of increased toxicity.[60]

9.1.2.3.1 Cycle 1- amended

For "tablet bridging cohort" or "food effect assessment" only:

Day -3 to Day -1 (possible overnight stay)

Day -3

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature and body weight
- Triplicate 12-lead ECG readings (see Section 9.5.3.4).

[59] Part 3 was added by Amendment 7, see section 15.6.2.20

[60] Added by Amendment 6, see section 15.6.2.21

- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Table 16-4
- Calculation of eGFR (see Section 16.9)
- Single oral administration of BAY 1163877 tablet formulation ("tablet bridging cohort" only)
- Single oral administration of BAY 1163877 tablet formulation immediately after consumption of high-fat, high-calorie meal as specified in Section 8.4.2.2.1 ("food effect assessment" only)
- PK sampling
- Toxicities / AE assessment and recording (if applicable)

Day -2

- No administration of BAY 1163877 ("drug-free day")
- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature
- Triplicate ECG readings (see Section 9.5.3.4)
- ECOG performance status
- PK sampling
- Toxicities / AE assessment and recording (if applicable)

Day -1

- No administration of BAY 1163877 ("drug-free day")
- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature
- ECOG performance status
- PK sampling

- Toxicities / AE assessment and recording (if applicable)

Days 1-3 (possible overnight stay)

Day 1

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature and body weight (measurement of weight not required for subjects in the "tablet bridging cohort" and for subjects with "food effect assessment")
- Single 12-lead ECG reading (see Section 9.5.3.4)
- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Section 16.2.
- Calculation of eGFR (see Section 16.9)
- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and approximately 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)[61]
- Urine collection for PK analysis (to be performed in approximately 8 subjects in Part 1 or Part 2 MTD expansion cohorts, see Section 9.4.2.1)
- Dispense of study medication (BAY 1163877) and diary

→ **Oral administration of BAY 1163877 (single dosing for subjects with PK assessment, twice daily dosing for subjects without PK assessment and for subject in Part 3)[62]**

→ **Oral administration of a single dose of BAY 1163877 after at least 8 hours of overnight fast as specified in Section 8.4.2.2.1 ("food effect assessment" only)**

- Toxicities / AE assessment and recording (if applicable)

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[61] Modified by Amendment 7, see section 15.6.2.22

[62] Part 3 added by Amendment 7, see section 15.6.2.22

Day 2

No administration of BAY 1163877 ("drug-free day") for subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects with PK assessment in study Part 2 and approximately 8 subjects with PK assessment in the MTD expansion cohorts with impaired renal function at baseline [including "food effect assessment"])[63]

- **Twice daily administration of BAY 1163877** for subjects without PK assessment (remaining subjects of study Part 2) and for subjects of Part 3[64]
- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature
- Single ECG reading (see Section 9.5.3.4)
- ECOG performance status
- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and approximately 8 subjects of the MTD expansion cohorts with impaired renal function at baseline) [65]
- Toxicities / AE assessment and recording (if applicable)

Day 3

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature
- ECOG performance status
- *Only for subjects included in study Part 1*/ dose escalation *(all comer):* Blood (serum) samples collection for biomarker investigations, see Table 16-5
- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 andapproximately 8 subjects of the MTD expansion cohorts with impaired renal function

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[63] Modified by Amendment 7, see section 15.6.2.22

[64] Part 3 added by Amendment 7, see section 15.6.2.22

[65] Modified by Amendment 7, see section 15.6.2.22

at baseline)[66]

- Dispense of study medication (BAY 1163877) and diary

→ Oral administration of BAY 1163877

- Toxicities / AE assessment and recording (if applicable)

[66] Modified by Amendment 7, see section 15.6.2.22

Day 8 ± 1 (Visit)

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature
- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Section 16.2.
- *Only for subjects in Part 3*: Collection of peripheral blood for determination of cytokine levels[67]
- Calculation of eGFR (see Section 16.9)
- Dispense of study medication (BAY 1163877) and diary

→ Oral administration of BAY 1163877

- Toxicities / AE assessment and recording (if applicable)

Days 15 (Visit)

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature
- ECG reading (see Section 9.5.3.4)
- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Section 16.2.
- Calculation of eGFR (see Section 16.9)
- PK sampling (all subjects of study Part 1, 3 and at least 12 subjects of study Part 2 and approximately 8 subjects of the MTD expansion cohorts with impaired renal function

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67 Added by Amendment 7, see section 15.6.2.22

at baseline)[68]

- Dispense of study medication (BAY 1163877) and diary

→ Oral administration of BAY 1163877

- Toxicities / AE assessment and recording (if applicable)

9.1.2.3.2 Subsequent Cycles (Cycles 2-12) - amended

Day 1 (Visit)

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature and body weight
- 12-lead ECG, single reading (see Section 9.5.3.4)
- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Section 16.2.
- *Only for subjects in Part 3 in Cycle 2:* peripheral blood sample collection for determination of cytokine levels. [69]
- Calculation of eGFR (see Section 16.9)
- Only on Day 1 of Cycles 2, 3, 4 and 5: Blood (plasma) sample collection for exposure-response modeling at pre-dose and between 0.5 and 1.5 hours post-dose in all subjects participating in the MTD expansion cohorts of study Part 1, Part 2, and Part 3 (not in subjects with impaired renal function) , see Table 16-3. The dose needs to be taken under supervision and the time recorded. [70]
- Only on Day 1 of Cycle 2: Obtain second biopsy: mandatory for all subjects in the MTD expansion cohort of Part 1 (all comer), voluntary for subjects in the dose escalation cohorts of study Part 1 (all comer) and in the MTD expansion cohort of Part 2, and send to laboratory, see Section 16.2.[70]
- Mandatory for all subjects in study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC): Between Day 1 and Day 21 of Cycle 2: Obtain second biopsy

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[68] PK sampling in part 3 added by Amendment 7, see section 15.6.2.22

[69] Part 3 was added by Amendment 7, see section 15.6.2.23

[70] Modified by Amendment 7, see section 15.6.2.23

and send to laboratory, see Section 16.2; obtain peripheral blood for determination of cytokine levels. Subjects in Part 3 will provide one PK sample within 1 hour of biopsy collection in Cycle 2. [71]

- Dispense of study medication (BAY 1163877) and diary

→ Administration of BAY 1163877

- Toxicities / AE assessment and recording (if applicable)

Day 8 ± 1 and Day 15 ± 1 (Visits)

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Section 16.2.
- *Only for subjects in Part 3 on Day 15 in Cycle 2:* peripheral blood sample collection for determination of cytokine levels.[72]
- Calculation of eGFR (see Section 16.9)

→ Oral administration of BAY 1163877

- Toxicities / AE assessment and recording (if applicable)

End of Cycle 2 and every 2nd subsequent Cycle (i.e., end of Cycles 2, 4, 6, 8, 10, 12)

- Send subject to consultant ophthalmologist for ophthalmological examination and review certificate

End of Cycle 2 and every 3rd subsequent Cycle (i.e., end of Cycles 2, 5, 8, 11)

- CT scans of the chest, abdomen and pelvis; CT scans of other metastatic lesions as applicable or MRI and documentation of response according to RECIST, v1.1 (see Section 9.3.1)

9.1.2.3.3 Subsequent Cycles (Cycles ≥13)

Day 1 (Visit)

- Update of concomitant therapy

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[71] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.23

[72] Added by Amendment 7, see section 15.6.2.23

- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature and body weight
- 12-lead ECG, single reading (see Section 9.5.3.4)
- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Section 16.2
- Calculation of eGFR (see Section 16.9)
- Oral administration of BAY 1163877
- Toxicities / AE assessment and recording (if applicable)

Day 11 (Visit)

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Section 16.2.
- Calculation of eGFR (see Section 16.9)
- Oral administration of BAY 1163877
- Toxicities / AE assessment and recording (if applicable)

End of Cycle 14 and every 2nd subsequent Cycle (i.e., end of Cycles 14, 16, 18, …)

- Send subject to consultant ophthalmologist for ophthalmological examination and review certificate

End of Cycle 14 and every 3rd subsequent Cycle (i.e., end of Cycles 14, 17, 21, …)

- CT scans of the chest, abdomen and pelvis; CT scans of other metastatic lesions as applicable or MRI and documentation of response according to RECIST, v1.1 (see Section 9.3.1)

9.1.2.3.4 Follow-up

An End of Treatment (EOT) visit will be performed within 0-14 days after the last study drug administration.

A follow-up (FU) visit will be performed 30-35 days after the last study drug administration. This will be a visit for subjects who have not started a new treatment. For subjects who have started a new antitumor treatment, only a phone call will be made. There will be no long-term (survival) follow-up period.

The following examinations will be done

Within 0-14 Days of Last Study Drug Administration (EOT Visit)

- Update of concomitant therapy
- Return of study medication and diary
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature and body weight
- 12-lead ECG, single reading (see Section 9.5.3.4)
- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Section 16.2.
- Calculation of eGFR (see Section 16.9)
- Send subject to consultant ophthalmologist for ophthalmological examination and review certificate
- Toxicities / AE assessment and recording (if applicable)

At 30-35 days after last study drug administration: FU (Visit / Phone call)

<u>If FU-visit:</u>

- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Toxicities / AE assessment and recording (if applicable)

<u>If FU-phone call*</u>

Toxicities / AE assessment and recording (if applicable)

*For subjects who have started a new antitumor treatment.

9.2 Population characteristics

9.2.1 Demographic

The following information will be collected and summarized as part of the demographic and baseline characteristics for all subjects enrolled in this study: age, gender, ethnic group. The subjects of all races / ethnicity can participate in the study provided that they meet all eligibility criteria.

9.2.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant to the study

Detailed instructions on the differentiation between medical history and AEs can be found in Section 9.5.1.1.

9.2.3 Other baseline characteristics

Other baseline characteristics to be obtained include

- Tumor stage according to the International Union Against Cancer (UICC), Tumor Node Metastasis (TNM) Classification of Malignant Tumors, 7th edition (UICC-TNM v 7, see Section 16.6).
- Presence of visceral or non-visceral metastases in subjects with metastatic disease
- Prior therapy received for locally advanced or metastatic solid tumors:
  - Neoadjuvant therapy: Treatment (e.g. chemotherapy, radiation therapy, and hormone therapy) given as a first step to shrink a tumor before the main treatment, usually surgery.
  - Adjuvant therapy: Additional cancer treatment given after the primary treatment to lower the risk of cancer recurrence (e.g., chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy).
  - Any other anticancer therapy (to be specified in the eCRF)
- Smoking habits and alcohol consumption.

9.3 Efficacy

Efficacy will be assessed by determining tumor response to therapy as a secondary endpoint.

For each subject, the investigator will designate at least 1 and up to 5 measurable (if appropriate) or non-measurable lesions for response assessment. The most appropriate

measures to evaluate the tumor status of a subject should be used. The investigator must enter a statement in the subject's medical records clearly defining the basis of his / her decision on subject disease status.

The following standard assessments should be performed to evaluate the response of the tumors:

- Tumor response assessment for measurable lesions (CT / MRI scan) according to RECIST, v1.1, see Section 9.3.1

All records and films of responding subjects (complete response, partial response, and stable disease) must be available for eventual extramural review of the tumor.

All measurable and evaluable disease will be assessed by the identical method as used at baseline. All measurements should be recorded in metric notation, using a ruler or calipers.

9.3.1 Tumor evaluation - response assessment (RECIST)

In *measurable* lesions (i.e., at the primary site, visceral or nodal [in lymph nodes ≥ 1,5 cm] lesions), the objective response will be assessed by CT / MRI scan at the EOT visit and documented according to the revised RECIST guideline, Version 1.1 (RECIST, v1.1), see Section 16.8. The assessment will be done by the investigators. No central evaluation is planned for this study.

CT / MRI scans will be performed at the following time points:

- Screening (within 28 days prior to the first dose of BAY 1163877)
- At the end of Cycle 2 and every third subsequent Cycle (beginning with Cycle 5)

Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluation of tumor response.

A zero should be recorded when a lesion has completely resolved. Otherwise, disappearance of a lesion cannot be differentiated from a missing value.

The occurrence and location of new lesions should be recorded in the eCRF and the subject's medical records.

In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Section 16.8).

If radiographic changes are believed by the investigator to be secondary to drug induced inflammation and not tumor progression, the investigator may postpone a diagnosis of progressive disease (PD) until the next radiographic evaluation in the study.

All scans should be done with the identical modality (CT or MRI) and the identical technique (e.g., slice thickness, field of view) to those obtained at baseline. For a response to be scored as complete response (CR) or partial response (PR), the response must be confirmed by a repeat CT scan (with contrast) or MRI scan (with and without contrast) performed not earlier than 4 weeks after the response was first determined.

9.4 Clinical pharmacological parameters and procedures

9.4.1 Pharmacodynamics

9.4.1.1 Cardiovascular assessment

To assess a possible pharmacodynamic effect of BAY 1163877 on cardiovascular function, a blood pressure (BP) / heart rate (HR) profile will be recorded by an automated device as follows:

- Subject seated for at least 2 minutes before measurement with their arms bared and supported at heart level.
- At screening, BP must be measured in both arms to see whether there is a difference in blood pressure readings between the subject's right and left arm. If one arm has higher blood pressure than the other, that arm should be used for further BP measurements (all further BP measurements must be done on the same arm)
- When blood pressure measurement and PK sample collection are scheduled at the same time point, subject's blood pressure will be measured before collection of the PK sample.

BP and HR will be measured at the following time points:

- Screening (one measurement within 7 days before start of treatment)
- Cycle 1, Day -3 to Day -1 ("tablet bridging cohort" and "food effect assessment" only)
  - before and 0.5, 1, 2, 3, 4, 6, 8, 12 (Day -3), 24 (Day -2) and 48 (Day -1) hour(s) after single-dose administration
- Cycle 1, Day 1 and Day 2

  before and 0.5, 1, 2, 3, 4, 6, 8, 12 (Day 1), and 24 (Day 2) hour(s) after single-dose administration
- Cycle 1, Day 3
  - before and 1, and 2 hour(s) after morning dose
- Cycle 1, Day 8 (one measurement)
- Cycle 1, Day 15
  - before and 0.5, 1, 2, 3, 4, 6, 8 and 12 hour(s) after morning dose (12-hour measurement before evening dose)
- Cycle ≥ 2 and follow up
  - each visit (one measurement)
- Follow up

  EOT visit (one measurement)

FU-visit (one measurement)

If a reduction of systolic BP below 90 millimeters of mercury (mmHg) or an increase in HR above 120 beats per minute (bpm) is detected, the assessment has to be repeated after 2 hours.

When blood pressure measurement and PK sample collection are scheduled at the same time point, subject's blood pressure will be measured before collection of the PK sample.

Details about ECGs readings are provided in Section 9.5.3.4.

9.4.1.2 Assessment of immune priming[73]

Assessment of immune response will be done at screening and during treatment for subjects in the "Safety cohort" (Part 3: sqNSCLC + LAC + BC). For gene expression profiling (nCounter PanCancer Immune Profiling Panel) and immunohistochemistry for CD8+ T cell infiltration and PD-L1 expression a fresh tumor biospy (e.g. obtained by endoscopic or ultrasound guided biopsy) will be collected as follows:

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

  Screening: Biopsy is mandatory

  Between Cycle 2, Day 1 and Cycle 2, Day 21: Biopsy is mandatory

Peripheral blood will be collected for determination of cytokine levels (IL-6, IFN-gamm, and others if needed) at the following timepoints: at baseline; Cycle 1, Day 8; Cycle 2, Day 1; Cycle 2, Day 15; and on the day of the second biopsy.

9.4.2 Pharmacokinetics

9.4.2.1 Drug measurements - amended

Pharmacokinetics of BAY 1163877 will be evaluated on Cycle 1, Day -3 ("tablet bridging cohort" and "food effect assessment", only), on Cycle 1, Day 1 after single-dose administration, and on Cycle 1, Day 15 after multiple-dose administration of BAY 1163877 at the respective dose level achieved during dose escalation.

Pharmacokinetic assessments will be performed in all subjects enrolled in Part 1 (dose escalation and MTD expansion (all comer) cohorts). The plan is to perform pharmacokinetic assessments in at least 12 subjects in Part 2 MTD expansion cohort (sqNSCLC + LAC + BC + SCCHN) such that valid PK data are available in 8 subjects. "Food effect assessment" will be performed in approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2). In the MTD expansion cohorts pharmacokinetic assessments will be performed in approximately 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated

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[73] Whole section - immune priming - was added by Amendment 7, see section 15.6.2.24

formula). In all subjects participating in study Part 3/ MTD expansion "Safety cohort", multiple dose pharmacokinetics (on Cycle 1 Day 15) will be performed.[74]

Blood (plasma) samples for PK assessment of BAY 1163877 will be collected at the following time points:

- Cycle 1, Day -3 ("tablet bridging cohort" and "food effect assessment" only): single-dose PK
  - pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hour(s) post-dose
- Cycle 1, Day 1: single-dose PK
  - pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hour(s) post-dose (48-hours sample before administration of morning dose on Day 3)
- Cycle 1, Day 15: multiple-dose PK
  - pre-dose (before morning dose), and 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post-dose (12-hours sample before administration of evening dose)
- Cycles 2-5, Day 1: exposure-response modeling (not in subjects with impaired renal function)
  - pre-dose (before supervised dose administration), and 1 (± 0.5) hour post-dose
- Cycle 2: Subjects in Part 3/ MTD expansion "Safety cohort" will provide one PK sample within 1 hour of biopsy collection in Cycle 2.[75]

In consultation with the investigators, if needed, up to three additional samples may be collected during the study.

Whenever possible, all efforts should be made to adhere to the blood sampling schedule as given above. However, based on practical considerations, the following time range is provided: for planned time points ≤ 6 hours, PK samples should be collected within ±15 minutes of the planned time, and for planned time points > 6 hours, PK samples should be collected within ±30 minutes. Sampling times outside the suggested intervals will not be considered as protocol deviations. It is of importance that the actual date and time of blood sampling is documented in the eCRF and subject`s source document because PK calculations will be based on the actual sampling times relative to dosing times.

When blood pressure measurement and PK sample collection are scheduled at the same time point, subject's blood pressure will be measured before collection of the PK sample.

24-hour urine collection: In approximately 8 subjects of the MTD expansion cohorts (study Part 1 and Part 2), on Cycle 1 Day 1, complete urine output will be collected over

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[74] Modified and Part 3 added by Amendment 7, see section 15.5.2.2015.6.2.25

[75] Part 3 added by Amendment 7, see section 15.5.2.2015.6.2.25

24 hours post administration in 0 to 12 hour and 12 to 24 hour intervals concurrently with plasma PK samples. For each subject, within each collection interval, the collected urine will be combined and the total volume of the combined urine will be determined.
A representative aliquot of the pooled urine will be used to determine the concentration of BAY 1163877.

Plasma and urine concentrations of BAY 1163877 will be measured using a validated method. Instructions for sample collection, processing, storage and shipment will be described in a separate document (e.g. lab manual).

Exploratory monitoring of metabolites may also be performed in pooled plasma samples (most likely at the MTD or the therapeutic dose) and in urine samples.

9.4.2.2 Pharmacokinetic evaluation

PK parameters will be calculated by non-compartmental analysis (NCA) according to current Bayer guidelines using WinNonlin software, in the latest version. PK parameters from NCA will be evaluated only for those subjects meeting the PK validity criteria (Section 10.2). Based on plasma concentration versus time results, the following parameters are planned to be calculated (see Table 9-1):

Table 9-1: Pharmacokinetic parameters to be evaluated for BAY 1163877

Symbol	Definition
%AUC(t_{last}-∞)	percentage of AUC from the last data point > LLOQ to infinity
AUC	area under the plasma concentration vs. time curve from zero to infinity after first dose
AUC(0-12)	AUC from time zero to 12 hours after first-dose administration
AUC(0-12)/D	AUC(0-12) divided by dose
AUC(0-t_{last})	Area under the concentration-time curve from time zero to the last data point > LLOQ
AUC(0-t_{last})/D	AUC(0-t_{last}) divided by dose
AUC/D	AUC divided by dose
C_{max}	maximum drug concentration in plasma after first dose administration
C_{max}/D	maximum drug concentration in plasma at steady state divided by dose (mg)
Md	multiple dose
$t_{1/2}$	half-life associated with the terminal slope
t_{last}	time of last plasma concentration above LLOQ
t_{max}	time to reach maximum drug concentration in plasma after single (first) dose

Primary PK parameters (plasma): **BAY 1163877**

- **Cycle 1, Day -3 ("tablet bridging cohort" and "food effect assessment" only) and Cycle 1, Day 1 single dose:** C_{max}, C_{max}/D, AUC(0-12), AUC(0-12)/D, AUC(0-t_{last}), AUC(0-t_{last})/D, AUC, and AUC/D
AUC may not be calculated if it is not possible to estimate half-life.

- **Cycle 1, Day 15 multiple dose:** $C_{max,md}$, C_{max}/D_{md}, $AUC(0\text{-}12)_{md}$, $AUC(0\text{-}12)/D_{md}$, $AUC(0\text{-}t_{last})_{md}$, and $AUC(0\text{-}t_{last})/D_{md}$.

Secondary PK parameters (plasma): **BAY 1163877**

- t_{max}, t_{last}, $t_{1/2}$ of Cycle 1, Day -3 ("tablet bridging cohort" only) and Cycle 1, Day 1 and $t_{max,md}$ and $t_{last,md}$ of Cycle 1, Day 15.

Other PK parameters (plasma): **BAY 1163877**

- $\%AUC(t_{last}\text{-}\infty)$

Additional parameters, e.g. apparent oral clearance (CL/F) and apparent volume of distribution at steady state after extravascular administration (Vss/F), may be estimated, if appropriate.

Pre-dose plasma concentrations (if additionally collected) will be used for monitoring purpose only.

Amount of BAY 1163877 excreted renally during 0 to 12 h ($A_{E,ur}(0\text{-}12)$), 12 to 24 h ($A_{E,ur}(12\text{-}24)$) and 0 to 24 h ($A_{E,ur}(0\text{-}24)$) post-dose will be calculated at the MTD and also expressed as percent of dose administered.

Pharmacokinetic evaluation - Population analysis

Pharmacokinetic data might be analyzed using nonlinear mixed effects models. Details of the model development and evaluation will be described in a separate Evaluation Plan and the results reported in a separate Evaluation Report.

These samples collected on Day 1 of Cycles 2 through 5 at pre-dose and between 0.5 and 1.5 hours post-dose will document a longitudinal exposure under steady state condition. No detailed dosing history is required before the pre-dose sample, but the dose that separates the pre- and post-dose sample needs to be taken under supervision and the time recorded. The longitudinal exposure data will be used in exposure-response modeling of adverse events and clinical responses.

9.4.3 Safety Variables

Please refer to Section 9.5.3

9.4.4 Biomarker investigations - amended

Concentrations of FGF23 will be measured by a validated ELISA assay. Instructions for sample collection, processing, storage and shipment will be described in a separate document (e.g. lab manual).

Pharmacodynamic (PD) biomarkers:

In an attempt to demonstrate the mechanism of action of BAY 1163877, biomarkers will be studied in tissue samples.

Biomarker analysis in TUMOR TISSUE

Biomarker analysis will be done at pre-screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN; Part 3 sqNSCLC + LAC + BC) according to FGFR expression levels / FGFR mutation using either an archival tumor tissue specimen or fresh tumor biopsy material (see Section 7.1.1: Inclusion criteria, and Section 9.4.4.1: Predictive marker investigation).[76] For analysis of phospho-extracellular signal-regulated kinase 1/2 levels, (p-ERK1/2) a tumor biospy (e.g. obtained by endoscopic or ultrasound guided biopsy) will be collected as follows:

- Study Part 1 / dose escalation (all comer):
  - Screening: Biopsy is optional* (p-ERK1/2)
  - Cycle 2, Day 1: Biopsy is optional* (p-ERK 1/2)
- Study Part 1 / MTD expansion (all comer):
  - Screening: Biopsy is mandatory (p-ERK1/2)
  - Cycle 2, Day 1: Biopsy is mandatory (p-ERK1/2)
- Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN):

  Screening: Biopsy is optional* (p-ERK1/2)

  Cycle 2, Day 1: Biopsy is optional* (p-ERK1/2)

*Optional biopsy: Only for subjects who agreed on biopsy both at screening and on Cycle 2, Day 1.

Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy for biomarker (p-ERK1/2) studies is taken.[77] Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

The evaluation of FGFR pathway mutations is planned retrospectively for subject in the MTD expansion cohorts.

Tumor response evaluation: Computed tomography (CT) or magnetic resonance imaging (MRI) of all anatomic regions involved with the disease will be performed at screening (baseline), at the end of Cycle 2 and thereafter, every third cycle to assess tumor response using the Response Evaluation Criteria in Solid Tumors, Version 1.1. (RECIST v1.1)(1). Response evaluation according to RECIST v1.1 can be done up to 5 days after CT / MR

[76] Part 3 added by Amendment 7

[77] Modified by Amendment 7, see section 15.6.2.26

scan.

Rationale for serum FGF23, phosphate and calcium measurements as PD biomarker

The phosphaturic hormone fibroblast growth factor 23 (FGF23) controls phosphate homeostasis by regulating renal expression of sodium-dependent phosphate co-transporters (18). Multiple FGF receptors (FGFRs) can act as receptors for FGF23 when bound by the co-receptor Klotho expressed in the renal tubular epithelium. FGFRs also regulate skeletal FGF23 secretion (19). Activation of FGFR-FGF23 signaling, e.g. by administration of an FGFR1 activating antibody (20) or by administration of recombinant FGF23 to mice (21) leads to hypophosphatemia. Likewise, inhibition of renal FGFR signaling e.g., by administration of pan-FGFR kinase inhibitor leads to an enhanced reabsorption of phosphate in the kidney and thus to an increase of serum phosphate levels. This increase of phosphate levels in turn activates FGF23 synthesis in the bone leading to higher serum levels of FGF23 (22). The FGF23/FGFR/Klotho complex also limits renal vitamin D synthesis and thus intestinal calcium uptake (23)(24). FGFR inhibitor treatment may therefore lead to increased serum calcium levels. Hence, modulation of circulating FGF23, and the incidence of hyperphosphatemia and elevated serum calcium levels are potential biomarkers for effective systemic FGFR inhibition (25). A dose-dependent hyperphosphatemic effect accompanied by an increase of serum FGF23 levels was observed in all animal species after BAY1163877 administration including mouse, rat and monkeys. Similar effects have also been observed with competitor compounds in preclinical models (26)(22) and in clinical trials (28)(29).

Rationale for the immunohistochemical quantification of tumor p-ERK levels as PD biomarker

Activation of the FGFR signaling pathway leads to enhanced cell proliferation – an effect that is mediated at least in part by Extracellular Regulated Kinases 1&2 (ERK1/2) (27). In a large set of human tumor cell lines, the phosphorylation of p-ERK1/2 was increased upon stimulation of the FGFR signaling pathway with the FGFR ligand bFGF, whereas pre-treatment of the cells with pan-FGFR inhibitor BAY 1163877 strongly reduced p-ERK1/2 phosphorylation levels and inhibited cell proliferation. In line with this, treatment of tumor-bearing xenograft mice with pan-FGFR-inhibitor BAY 1163877 leads to a reduced phosphorylation of tumor ERK1/2 in sensitive models, whereas no effect or only a weak effect on tumor p-ERK1/2 levels was observed in xenograft mouse models that were largely insensitive to BAY 1163877-treatment. Quantification of tumor p-ERK1/2 levels in biopsy samples from study participants pre- and post-treatment with BAY 1163877 may thus serve as an early predictor of clinical efficacy of the drug, as has been described for many kinase inhibitors in first-in-man trials including competitor compound dovitinib (28)(29).

9.4.4.1 Predictive marker investigations - amended

Prediction Biomarker:

For subjects to be enrolled in study Part 1 / MTD expansion (all comer), subjects to be enrolled in Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) and subjects to be enrolled in Study Part 3 MTD expansion (sqNSCLC + LAC + BC)

biomarker analysis will be done prior study start (subject stratification) on either a fresh or archival tumor biopsy sample to confirm high fibroblast growth factor receptor (FGFR) expression levels / FGFR mutation (see Section 7.1.1: Inclusion criteria). [78]

Rationale for the quantification of tumor FGFR-1 -2- and -3 levels

Amplification of the FGFR1 8p12 gene locus has been observed in up to 20 % of sqNSCLC subjects (8)(9)(11). FGFR1 gene amplification is so far one of the most frequently observed molecular alteration in sqNSCLC (30). In SCCHN, the FGFR1 gene was amplified in about 15 % of all cases (38). *In vitro* experiments with BAY 1163877 and published data with competitor compounds revealed equal sensitivity to proliferation inhibition by either adenocarcinoma or squamous subtype-derived lung cancer cell lines. In-house quantification of FGFR1-3 mRNA expression levels in patient-derived lung cancer tumors revealed a high FGFR1, 2 or 3 mRNA expression levels also in cases of lung adenocarinomas. In line with this, a recent publication confirmed a strong expression of FGFR1 mRNA also in adenocarcinoma biopsy samples in the absence of FGFR1 amplification (39). Therefore, we suggest to include lung adenocarcinoma patients into Part 2 of the study. Mutations in FGFR-encoding genes are rare in sqNSCLC subjects (< 2%), whereas in bladder cancer, up to 70% of all cases reveal mutations within FGFR3 gene (31). The molecular consequences of FGFR gene amplifications are not always clear: In bladder cancer, activating FGFR3 mutations with higher kinase activity have been described (32) but also cases in which FGFR3 amplification leads to higher target expression levels in tumor (33).

Recent publications investigating the correlation between FGFR1 gene amplification in sqNSCLC and their correlation with target expression level (mRNA or protein expression) revealed, a high proportion of subjects with FGFR1 overexpression in tumor that do not have an FGFR1 gene amplification and even in those subjects with a high FGFR1 gene copy number, a relevant subset of subjects does not reveal high FGFR1 target overexpression (12)(13).

In line with this literature data on subject biopsy samples, preclinical *in vivo* data with competitor compound AZD4547 and *in vitro* data with competitor compound BGJ398 revealed that a correlation with response-to-treatment (tumor weight inhibition or proliferation inhibition) correlated only weakly with gene amplification status and that up to 50 % of tumor cells did not respond to FGFR inhibitor treatment despite having FGFR genetic alterations (10)(34). In house data revealed that the best correlation with anti-tumor efficacy upon BAY1163877-treatment in preclinical cancer models was observed for total-FGFR mRNA tumor expression levels - including lung and bladder cancer, and head and neck squamous cell cancer models. This may at least in part be explained by the parallel expression of more than one FGFR isoform in xenograft tumors which could not be investigated on protein level by immunohistochemistry due to the lack of isoform-specific, sensitive anti-FGFR antibodies. Parallel quantification of FGFR1/2/3 mRNA

[78] Part 3 added by Amendment 7

levels in fresh frozen xenograft tumors (by RT-PCR) and in archival tissue samples derived thereof (by RNA in situ hybridization) indicated a high degree of correlation between both methods. Thus, quantification of FGFR1/2/3 mRNA levels in archival tissue samples is technically feasible. We therefore consider to stratify sqNSCLC, LAC, BC and SCCHN subjects to be enrolled in study Part 2 and Part 3 / MTD expansion by the quantification of total FGFR mRNA expression levels in archival tissue samples in order to exclude subjects that are unlikely to benefit from BAY1163877 therapy due to low overall FGFR target expression levels.[79]

Rationale for the detection of genetic alterations in FGFR encoding genes and in FGFR pathway downstream signaling molecules

In subjects included in study Part 1 / MTD expansion (all comer) and Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) and Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC), genetic testing of tumor tissue may be necessary if a subject lacks a treatment response to BAY 1163877 despite FGFR overexpression in tumor. Such a lack of anti-tumor response upon BAY 1163877-treatment has been observed in some preclinical models despite high total FGFR mRNA tumor levels and may be attributable to a constitutively active FGFR downstream signaling pathway e. g. due to K-ras mutations. Existence of such FGFR downstream pathway activating mutations in the case of lack of response to BAY 1163877 treatment - despite high total FGFR mRNA tumor expression levels - should be evaluated retrospectively in subjects enrolled in study Part 1 / MTD expansion (all comer) and Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) and Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC).[80]

Furthermore, in some animal models with bladder cancer cell lines bearing an activating mutation in FGFR3 gene, a good anti-tumor response upon BAY 1163877-treatment was observed despite rather low overall total FGFR mRNA expression levels in tumor cells. We therefore consider genetic testing for FGFR3-activating mutations in bladder cancer subjects prior to treatment start - in case they lack high FGFR mRNA expression levels in tumor.

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[79] Part 3 added by Amendment 7

[80] Part 3 added by Amendment 7

9.5 Safety

9.5.1 Adverse events

9.5.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE).

- The clinical manifestation of any failure of expected pharmacological action (tumor progression) is not recorded as an AE. If, however, the event fulfills any of the criteria of an SAE, it must be recorded and reported as such unless otherwise specified in the protocol.

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g. physical examination findings, symptoms, diseases, laboratory values, ECG.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).

- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis).

- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

Serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a) Results in death

b) Is life-threatening

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

c) Requires insubject hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

The admission results in a hospital stay of less than 12 hours

The admission is pre-planned
(i.e. elective or scheduled surgery arranged prior to the start of the study)

The admission is not associated with an AE
(e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependant on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

a) Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

b) Is a congenital anomaly / birth defect

c) Is another medically important serious event as judged by the investigator

All SAEs occurring after the IC for study treatment eligibility has been obtained, until the end of the follow-up period must be handled via this process. All serious diagnoses, symptom(s), sign(s) or finding(s) that have a start date after signing the IC must be recorded as SAEs. This also includes all serious events with a start date during the pre-treatment period for subject stratification (FGFR expression / FGFR mutation testing period), **in case an invasive procedure was performed to obtain tumor material.** A condition that was present before signing the IC for study treatment eligibility and worsens after signing the IC must also be recorded as an SAE if the serious criteria are met.

9.5.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.5.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.5.1.1

9.5.1.2.2 Intensity

The intensity / severity of an AE will be graded using the CTCAE v4.03, see Section 16.5. For events not listed in the CTCAE v4.03 the following scale will be used:

Grade 1 = Mild AE, transient in nature and generally not interfering with normal activities

Grade 2 = Moderate AE, sufficiently discomforting to interfere with normal activities

Grade 3 = Severe AE, prevents normal activities

Grade 4 = Life-threatening and / or disabling AE

Grade 5 = Results in death (fatal)

9.5.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no"

An assessment of "no" would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.

- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):

- Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.

- Underlying, concomitant, intercurrent diseases:
Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant medication or treatment:
The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

- The pharmacology and pharmacokinetics of the study treatment:
The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the

study treatment, coupled with the individual subject's pharmacodynamics should be considered.

9.5.1.2.4 Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no."

9.5.1.2.5 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

9.5.1.2.6 Other specific treatment(s) of AE

- None
- Remedial drug therapy
- Other

9.5.1.2.7 Outcome

The outcome of the AE is to be documented as follows:

- Recovered / resolved
- Recovering / resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.5.1.3 Assessments and documentation of adverse events

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the subject, will be documented (see Section 11.1 for details).

AEs will be documented event based (using the CTCAE v4.03 guidelines). The observation phase for AEs will start with signing the first Informed Consent and will end in general with the last visit of follow-up. All AEs identified after first IC during the pre-treatment period for subject stratification (FGFR expression / FGFR mutation testing period) will not be documented in the eCRF, in case no invasive procedure will be performed to obtain tumor material. Adverse events should be collected past 30-35 days after the study treatment stop for all AEs that were ongoing at the end of treatment as well as new SAEs (information may be obtained via phone call). The investigator is responsible for the grading of each category mentioned in Section 9.5.1.2.

Adverse events should be followed until resolution or stabilization unless, in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease.

If any subject dies within 30-35 days of last dose of study drug, the investigator will inform the sponsor and record the cause of death in detail within 24 hours on a SAE form.

A laboratory test abnormality considered clinically relevant, e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an AE. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

An isolated laboratory abnormality that is assigned grade 4, according to CTCAE v4.03 definition, is not reportable as an SAE; unless the Investigator assesses that the event meets standard ICH criteria for an SAE. CTCAE v4.03 Grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria. If an Investigator is in doubt about the applicable reporting obligations, he/she should consult with the study monitor for the Sponsor. CTCAE v4.03 Grade 4 laboratory abnormalities will be documented in the laboratory data and will be reviewed on a regular basis.

For all SAEs the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

9.5.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 9.5.1.1.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the ISF. This information will be updated as needed.

All SAEs occurring during the observation period defined in Section 9.5.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to the recipient detailed in the Key Study Personal List. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by submission of updated

reports to the designated recipient.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IECs / IRBs

Notification of the Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) about all relevant events (e.g. SAEs, <suspected, unexpected, serious adverse reactions (SUSARs)>) will be performed by the sponsor (or delegate) and / or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g. fatal or life-threatening SUSARs) according to all applicable regulations.

9.5.1.5 Expected adverse events

Expected adverse drug reactions (ADRs)

Overview listings of frequent events that have occurred so far in the clinical development of BAY 1163877 are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.5.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a study subject during the subject's participation in this study. The report should be submitted within the same timelines as a SAE, although a pregnancy per se is not considered a SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.

Bayer usually does not gather information of drug exposure via father, however, if those cases are reported, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used.

9.5.3 Further safety variables

9.5.3.1 Physical examination including weight

The physical examination (by means of inspection, palpation, auscultation) will be performed according to the schedule summarized in the flow chart of Section 16.1. This includes review of all organ systems, examination of pertinent organ systems, and vital signs.

For this examination, the investigator will assess / examine the following:

- General appearances
- Skin
- Eyes
- Ears, nose and throat
- Head and neck
- Lungs
- Heart
- Abdomen
- Lymph nodes
- Musculoskeletal system (including extremities and spine)
- Neurological findings

If indicated by the subject's history, the following will be examined by specialists, if applicable:

- Genito-urinary system
- Gynecological organs
- Rectum

Depending on criteria of relative timing (before or after signing IC), the findings of the physical examination have to be recorded as medical / surgical history or as an AE.

Body weight will be measured in the morning by a member of the investigator's team under the following conditions:

- Fasting state of the subject, empty bladder, without shoes, in underwear

Subject's body height in centimeter (cm) will be measured only at screening.

Subject's body mass index (BMI) is calculated at screening by dividing the subject's weight by the square of his or her height (kg/cm2).

A skin check for detection of hand-foot skin reaction (HFSR) will be performed by a physician at each study visit.

9.5.3.2 Ophthalmological examination

A complete ophthalmologic examination will be performed by an ophthalmologist, at screening, during treatment (every second cycle) and at the EOT visit. The exam will include previous eye history and any ophthalmic symptoms, best corrected visual acuity, dilated ophthalmoscopy and optical coherence tomography for the measurement of central foveal thickness. The ophthalmologist will describe examination findings on an examination worksheet provided by the investigational site. Any findings qualifying as an adverse event will be recorded accordingly.

Additionally, the investigator will ask the subject for changes in vision at each site visit.

9.5.3.3 Vital signs

Systolic / diastolic blood pressure, respiration rate and heart rate will be measured by a member of the investigator's team (cardiovascular assessment, see Section 9.4.1.1).

Body temperature will be measured by a member of the investigator's team according to the following method: sublingual, using an electronic thermometer with digital display and recorded in the eCRF in degree Celsius (°C).

9.5.3.4 Electrocardiogram (ECG)

For the assessment of possible drug effects on QT/ QTc interval duration at pre-defined time points at screening and in Cycle 1, standard 12-lead ECGs will be recorded in triplicates in selected subjects dosed with 50 mg and higher until implementation of Amendment 5. The triplicate ECGs will be recorded in close sequence and **not more than 2 minutes apart**.

Subjects will have a single ECG recording in all subsequent cycles.

12-lead ECG readings will be performed in the supine position at the following time points:

- Screening (single ECG readings)
- Cycle 1, Day -3 and Day -2 (triplicate ECG readings ["tablet bridging cohort" and "food effect assessment" only])
  - before and 2, 3 (Day -3) and 24 (Day -2) hours after single-dose administration
- Cycle 1, Day 1 and Day 2 (single ECG reading)
  - before and 2, 3 (Day 1) and 24 (Day 2) hours after single-dose administration
- Cycle 1, Day 15 (single ECG reading)
  - before morning dose, and 2 and 3 hours thereafter
- Cycle ≥ 2, Day 1 (single ECG readings)
  - after morning dose
- EOT visit (single ECG reading)

The study number, SNR, visit and the date of the ECG are noted on every ECG. All ECGs recorded during the study will be evaluated by a physician. He / she will document the diagnosis(-ses) including an overall assessment of the findings and their clinical relevance in the eCRF.

9.5.4 Echocardiography / MUGA scan

An echocardiography or MUGA (multiple gated acquisition) scan is to be done at screening (within 7 days prior to first study drug administration) to ensure that only

subjects with adequate cardiac function (LVEF ≥ 50%) participate in this study. This is no longer needed after implementation of Amendment 5. [81]

9.5.4.1 ECOG Performance status

Subject's ability to manage activities of daily living will be appraised utilizing the performance status scale by USA Eastern Cooperative Oncology Group (ECOG), see Section 16.7. The subject's ECOG performance score will be estimated according to the schedule summarized in the flow chart of Section 16.1. An ECOG Performance Status score of 0, 1 or 2 is required for study inclusion (see Section 7.1.1).

9.5.4.2 Laboratory examinations - amended

Section 16.2 provide the parameters and time points **for the laboratory examinations to be performed during the study.**

Blood and urine samples for the safety laboratory tests, biomarker investigations, and gene expression profiling and cytokine levels will be collected by a member of the investigator's team.[82]

The laboratory test results will be made promptly available to the investigator except for the biomarker parameters and cytokine levels, which will be analyzed in batches where appropriate.

Detailed information about the handling and labeling of the samples will be provided in a separate document (e.g. Laboratory Manual).

The following laboratory analyses (safety laboratory tests) will be performed by the local laboratory or at the study site (see Section 16.2):

Blood tests:

- Hematology and biochemistry parameters (for details see Section 16.2)

  Serum creatinine concentration will be used to estimate the subject's glomerular filtration rate (eGFR) at screening utilizing the Modification of Diet in Renal Disease (MDRD) equation, see Section 16.9.

  Coagulation parameters (for all subjects).

  Virology tests

Urine tests:

Macroanalysis

Urinalysis (dip stick and laboratory analysis), for details see Section 16.2.

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[81] Section 9.5.4 deleted by Amendment 5, see section 15.5.2.24

[82] Cytokines added by Amendment 7, see section 15.6.2.28

Microscopic analysis: to be performed if the appearance of urine is turbid, or if protein, leukocytes, erythrocytes, or nitrite are out of normal range.

Urine pregnancy test (**only in woman of childbearing potential**). Postmenopausal women who have not had periods for more than 1 year or surgically sterilized women will not be required to undergo a pregnancy test (this information should be recorded under medical history in the eCRF).

The following laboratory analyses will be performed by analysis laboratories:

Tumor biopsies:

- Quantification of tumor p-ERK levels pre- and post-treatment by immunohistochemistry
  In this clinical trial, tumor biopsies will be examined using immunohistochemistry in order to examine the relationship between tumor p-ERK and response to BAY 1163877 therapy. Paired tumor biopsies should be obtained prior to study treatment and on Cycle 2, Day 1 (at the end of Cycle 1) for analysis of p-ERK in tumor tissue.
- Quantification of tumor FGFR1, 2 and 3 mRNA levels
  In this clinical trial tumor biopsies will be examined for FGFR1, FGFR2 and FGFR3 mRNA levels from biopsy samples / archival biopsy samples.
- Retrospective evaluation of mutations in either FGFR encoding genes or in FGFR downstream pathway genes from biopsy samples / archival tissue samples.
- Gene expression profiling (nCounter PanCancer Immune Profiling Panel)
- Immunhistochemistry for CD8+ T cell infiltration and PD-L1 expression

Peripheral Blood:

- Collection of serum to determine cytokine levels (IL-6, IFN-gamma, and others if needed)[83]

Subjects with BC with low overall FGFR expression levels can only be included in study Part 2 or Part 3 if an activating mutation in FGFR3 gene has been confirmed at screening.

9.6 Other procedures and variables

9.6.1 Diary

Subject paper diaries in local language will be provided to the study sites, to document the following information:

Daily oral administration of BAY 1163877 (amount of drug and time of dosing) by the subject

[83] Gene expression profiling, immunohistochemistry and blood cytokines added in Part 3, see section 15.6.2.28

Confirmation of diary check by the investigator's team and clinical research assistant (CRA)

The daily records of study drug intake will be transferred to the database in accordance with the data entry guidelines.

The subject will be told to start the diary with the first oral administration of the study drug on Cycle 1 / Day 1. The subject has then to keep the diary until the end of the treatment period. The subject will be told to bring the diary along to each visit. The diaries will be checked at each visit for completeness and plausibility by a member of the investigator's team (see Section 8.7). Care should be taken that the (handwritten) entries are clearly legible.

9.7 Appropriateness of procedures / measurements

All efficacy and safety parameters, as well as the methods to measure them, are standard variables / methods in clinical studies and / or clinical and gynecological practice. They are widely used and generally recognized as reliable, accurate and relevant.

10 Statistical measures and determination of sample size

10.1 General considerations

Statistical analysis will be performed using SAS (statistical analysis system); the version used will be specified in the statistical analysis plan. All data will be listed and study summary tables will be provided where appropriate. Quantitative data will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. Where appropriate, summary statistics will be provided for the original data as well as for the change versus baseline. Graphical illustrations will be provided where appropriate. Frequency tables will be provided for qualitative data. Due to the exploratory character of this study, no confirmatory analysis will be done. All calculated p-values and confidence intervals are to be interpreted in the exploratory sense.

Data from patients who are transferred to a roll-over study may be pooled and analyzed together with the data from the study in which the patient was initially included. The results from these analyses will be reported separately.

10.2 Analysis sets

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

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

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.

10.3 Variables

Variables (primary and secondary) are specified in Section 9.4.

10.4 Statistical and analytical plans

10.4.1 Demographic and other baseline characteristics

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented by treatment arm. Frequency tables for qualitative data will be provided. Medical history findings will be summarized using MedDRA (Medical Dictionary for Regulatory Activities) terms.

10.4.2 Maximum tolerated dose

Individual listings and treatment summaries of dose limiting toxicities 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 analysis (see Section 16.4 for details) as well as non-informative priors will be used for this analysis in order 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)-intercept) / slope.

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

10.4.3 Adverse events

Individual listings of adverse events will be provided. The incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent drug-related adverse events (TEADRs), respectively, will be summarized by cohort in frequency tables using worst CTCAE v4.03 grade. Frequency tables will also be provided for the changes of worst CTCAE v4.03 grade after start of treatment versus baseline. In addition analysis will be done using MedDRA terms.

10.4.4 Safety parameters

Quantitative data (vital signs, ECG) 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. Frequency tables will be provided for qualitative data.

Laboratory data outside the reference range will be listed with abnormal values flagged. The incidence of laboratory data outside the reference range (low, high) will be summarized by cohort in frequency tables. The incidence of laboratory toxicities will be summarized by worst CTCAE v4.03 grade and by cohort. Frequency tables will be

provided for the changes of worst CTCAE v4.03 grade after start of treatment versus baseline.

10.4.5 Pharmacokinetic data

The concentration-times courses of all analytes will be tabulated for each cohort. 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 treatment 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} and 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. Amount and percent of drug excreted in urine will be described by arithmetic statistics, minimum, maximum and median.

To investigate dose proportionality, an explorative analysis of variance (ANOVA), including the factor cohort, will be performed on the log-transformed values of appropriate PK parameters calculated from single (where applicable) and multiple dose PK profiles.

In order to evaluate the relative bioavailability of the tablet formulation, tablet C_{max}/D, $AUC(0\text{-}t_{last})/D$ and AUC/D on Cycle 1, Day -3 will be compared to solution C_{max}/D, $AUC(0\text{-}t_{last})/D$, 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, $AUC(0\text{-}t_{last})/D$, AUC/D will be calculated by retransformation of the logarithmic data using the intra-individual standard deviation of the ANOVA.

In order to evaluate the food effect, BAY 1163877 C_{max} and $AUC(0\text{-}t_{last})$ on Cycle 1, Day -3 and C_{max} and $AUC(0\text{-}t_{last})$ on Cycle 1, Day 1 will be compared. The logarithms of C_{max} and $AUC(0\text{-}t_{last})$ will be analyzed using ANOVA including subject and food effects. 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 $AUC(0\text{-}t_{last})$ will be calculated by retransformation of the logarithmic data using the intra-individual

standard deviation of the ANOVA.

10.4.6 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.

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.

10.4.7 Efficacy data

Efficacy data, such as best tumor response, will be summarized using descriptive statistics and will be graphically displayed if appropriate. The correlation between pharmacodynamic 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) and time to progression (TTP).

Response as defined by RECIST v.1.1: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), see Section 16.8.

Progression-free survival (PFS) is defined as the time (days) from the date of the first dose of study drug to the date of the first observed radiological disease progression or death, whatever comes first. PFS for subjects without tumor progression at the time of analysis will be censored at their last date of tumor evaluation.

Time to progression (TTP) is defined as the time from start of study treatment until objective tumor progression; TTP does not include deaths.

10.5 Planned interim analysis

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”).[84]

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[84] Part 3 - Safety cohort - was added by Amendment 7, see section15.6.2.29

10.6 Further analysis described and reported under separate cover

In order to evaluate the exposure-response during 4 cycles, two blood samples will be collected on Day 1 of Cycles 2-5, one before and one after a supervised dose. The resulting longitudinal exposure data will be modeled together with occurrences of selected adverse events and documented clinical responses. Also longitudinally measured PD biomarkers will be modeled with this exposure data. Exposure-response models and simulations after alternative dosing schedules will be reported in a separate document.

10.7 Determination of sample size - amended

This is primarily a descriptive safety and tolerability Phase I trial. No formal sample size estimation is performed. The actual sample size required to adequately determine the MTD depends on the initial dose, rate of dose escalation and the observed dose-toxicity and dose / exposure-pharmacological relationships. Simulation studies have been performed to quantify the operational characteristics (i.e., precision of the MTD, sample size, number of subjects being over / under dosed) of the adaptive dose-escalation design under a number of plausible dose-DLT relationship scenarios. Results are provided in Section 16.4. Based on experience the chosen sample size of 3-9 subjects per cohort is considered to be sufficient to fulfill the objectives of the study.

In study Part 1 / MTD expansion (all comer), additional subjects will be included in order to gain more information about biomarkers (p-ERK1/2) in at least 20 evaluable subjects with any solid tumors.

In study Part 2 / MTD expansion, additional subjects will be included in order to obtain further safety and PK data at the MTD level in at least 20 subjects with sqNSCLC or LAC, at least 30, up to a maximum of 50 evaluable subjects with BC and at least 8 subjects with SCCHN.[85]

In study Part 3 / MTD expansion “Safety cohort”, additional subjects will be included to expand the safety database, to collect additional efficacy data, and to assess changes of immune parameters during treatment at the MTD level in approximately 20 subjects with sqNSCLC or LAC, and approximately 20 subjects with BC. [86]

11 Data handling and quality assurance

11.1 Data recording - amended

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the study site. Entries into the eCRF should be made as soon as possible.

A Source Document Checklist will be used at site to identify the source data for all points

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[85] Modified by Amendment 7, see section 15.6.2.30

[86] Part 3 - Safety cohort - was added by Amendment 7, see section 15.6.2.30

collected.

A CRO (Linical, formerly part of Nuvisan) provides the investigational site with access to an internet / web-based electronic data capture (EDC) computer system (termed "Inform"). Oracle has developed this system as a secured data entry tool that cannot be modified by investigative sites. The customized application for this protocol was developed by Linical and validated according to Lincical "Standard Operating Procedures". Edit checks and data logic checks are done at the point of entry and are validated by Linical. All data entered into the system is transferred to a secure server maintained by Linical.

Access to the Inform EDC system at the site, at Linical and at Bayer is password protected. Study access is granted to site personnel only after they have been trained in the use of the Inform EDC System by Linical personnel or after a web-based training, either at the investigational site or at the investigators' meeting. Linical and Bayer personnel are also required to complete the training program before they are allowed to access the system. All Inform EDC system training history is documented and maintained by Linical.

The Inform EDC System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, and the date and time it was made. This information is available both at the investigator's site and at Linical.

Data entries made in the Inform EDC screens are supported by source documents maintained for all subjects enrolled in this study.

- Results from pharmacokinetic analyses

  The results of drug concentration measurements will be provided as electronic data files and transferred to Data Management, where the information necessary for evaluation will be added (e.g. administration and sampling time points, demographic data). This data set will be evaluated by the responsible pharmacokineticist. The complete pharmacokinetic evaluation will then be retransferred to Data Management.

<u>Results from biomarker analyses</u>

The results of biomarker analyses will be provided by the laboratories as electronic data files and transferred to Data Management, where the data is mapped into the database.

<u>Results from ECG measurement</u>

A part of the ECG analyses will be performed by Nabios. Nabios will send the electronic data files to Data Management, where the data is mapped into the database.

- Data recorded during the FGFR expression / FGFR mutation testing period (MTD expansion cohorts only)

  Limited data will be recorded for all subjects in the FGFR expression / FGFR mutation testing period as described below:

  - Subject number

- Demographic data
- Cancer classification including primary diagnosis (all comer for study Part 1; sqNSCLC, LAC, BC or SCCHN for Part 2; sqNSCLC, LAC or BC for Part 3), complete medical / oncological history data and TNM classification[87]
- Life expectancy
- ECOG Performance Status
- Information on existence of an archival tumor biopsy specimen
- Details on collection of fresh tumor material (if applicable)
- Adverse event(s) only in case an invasive procedure will be performed to obtain tumor material after informed consent

• Data recorded from "only screened subjects (screening failures)" including pre-screening

For screening failures, all items listed below must be documented within the eCRF:

- Subject number
- Date of informed consent
- Date of birth
- Gender
- Reason for discontinuation
- Date of Last Visit

For screening failures with an SAE, the following information has to be added:

- Adverse event(s)
- Concomitant medication
- Medical history
- Other information related to the SAE (e.g. laboratory results)

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's / CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor / designee will monitor the site activity to verify that the:

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[87] Part 3 added by Amendment 7

Data are authentic, accurate and complete

Safety and rights of subjects are being protected

Study is conducted in accordance with the currently approved protocol

- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

The data collection tool for this study will be the validated electronic system by Oracle Inform©. Subject data necessary for analysis and reporting will be entered/ transmitted into a validated database that will follow the sponsor's requirements. Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded in the eCRF as well as for data from other sources (e.g. ECG).

For data coding (e.g. AEs, medication), Linical will transfer the verbatim terms and internationally recognized and accepted dictionaries will be used by the sponsor.

Bioanalytical results for pharmacokinetic evaluation will electronically be transferred from the Bioanalytical Department to Data Management using a predefined uniform file format. Data Management will include these data in the corresponding SAS data repository. Data Management will create a transfer file containing the bioanalytical results, demographic data, dosing data, and actual dosing and sample collection times and will electronically send this file to Bayer, Clinical Sciences. Clinical Sciences will calculate all pharmacokinetic parameters indicated in this protocol as described in Section 9.4.2.2. The finalized evaluation will electronically be transferred to Data Management where all data will be included in the corresponding SAS data repository. All electronic file transfer processes will follow validated procedures.

11.4 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the investigational site and of the study documents originating there. The investigator / institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s) / IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator / institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his / her time and the time of his / her staff to the auditor / inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.5 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Subject (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The investigator / institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The ISF is not to be destroyed without the sponsor's approval.

The investigator's contract will contain all regulations relevant for the investigational site.

12 Premature termination of the study

The sponsor has the right to close this study (or, if applicable individual segments thereof [e.g. treatment arms, dose steps, centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs);
    (If dose Level 1 is not tolerated, the trial will end.)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate, drop-out rate, data quality, protocol compliance) does not suggest a proper completion of the study within a reasonable time frame.
- Strategic reasons (e.g. the clinical development of the drug is stopped).

The investigator has the right to close his / her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions (e.g. IEC(s) / IRB(s); competent authority(ies); study center(s)) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner

Details for individual subject's withdrawal can be found in Section 7.2.1.

13 Ethical and legal aspects

13.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the clinical study protocol (CSP) will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IEC / IRB / sponsor approval / favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC / IRB / sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.2 Subject information and consent

All relevant information on the study will be summarized in 2 separate integrated subject information sheet and informed consent forms (SIS / ICFs) provided by the sponsor or the study center.

SIS / ICF for FGFR expression / FGFR mutation testing

For subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN, Part 3: sqNSCLC + LAC + BC), a separate SIS / ICF will be provided to subjects for FGFR expression / FGFR mutation testing. This separate SIS / ICF gives brief information on the study conduct, details on the tissue sample required to be taken to perform the tests along with information on possible risks. [88]

SIS / ICF for study treatment eligibility

All subjects who have interest to participate in this study (including those who are confirmed presenting the appropriate FGF receptor level, or - for bladder cancer subjects - who are confirmed carrying the FGFR mutation) will be provided the SIS / ICF for screening of study treatment eligibility no longer than 28 days prior to start of

[88] Part 3 added by Amendment 7, see section 15.6.2.32

study treatment.

Samples of the 2 SIS /ICFs are provided as a document separate to this protocol.

Based on the subject information sheet(s), the investigator or designee will explain all relevant aspects of the study to each subject prior to his / her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IEC / IRB has been obtained.

Each subject will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject voluntarily agrees to sign the informed consent form(s) and has done so, may he / she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form(s). The subject will receive a copy of the signed and dated form(s).

The signed informed consent statement(s) is (are) to remain in the ISF or, if locally required, in the subject's note / file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

The informed consent form(s) and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form(s). The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his / her participation in the study by signing the revised informed consent form(s). Any revised written informed consent form and written information must receive the IEC / IRB's approval / favorable opinion in advance of use.

13.3 Publication policy - amended[89]

The sponsor is interested in the publication of the results of every study it performs. All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator / institution.

The sponsor has committed to the global industry position on disclosure of information about clinical trials. The information regarding the CSP is made publicly available on the internet at www.clinicaltrials.gov.

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89 Name of the sponsor changed to Bayer AG

All data and results and all intellectual property rights in the data and results derived from the trial will be the property of the Bayer AG, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, whilst free to utilize data derived from the trial for scientific purposes, must discuss any publication with Bayer AG prior to release and obtain written consent of Bayer AG on the intended publication. Bayer AG recognizes the right of the investigator to publish the results upon completion of the trial. However, the investigator must send a draft manuscript of the publication or abstract to Bayer AG 30 days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between Bayer AG and the investigator(s), the contents of the publication will be discussed in order to find a solution that satisfies all parties.

13.4 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and / or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor, IEC / IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

14 Reference list - amended

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[90] Reference 40 was added by Amendment 7

15 Protocol amendments

15.1 Amendment 1

Date of amendment: 31 Oct 2013

15.1.1 Overview of changes

Modification 1: Use of a further drug formulation (tablet)

Rationale for introducing Modification 1

Studies have demonstrated the stability of a tablet formulation of BAY 1163877 which was developed for ease of administration. The switch from solution to tablet formulation is planned after relative bioavailability assessment of the tablet formulation planned in one of the dose escalation cohorts ("tablet bridging cohort").

List of all CSP sections affected by Modification 1:

- Synopsis
- Section 2
- Section 4
- Section 6.1
- Section 6.2
- Section 6.4.2.1
- Section 6.4.2.2
- Section 6.4.2.3
- Section 7.1.2.3
- Section 7.1.2.3.1
- Section 7.4.1.1
- Section 7.4.2.1
- Section 7.4.2.2
- Section 7.5.3.4
- Section 8.2
- Section 8.4.5
- Section 14.1
- Section 14.2

Modification 2: Completion of listing of primary variables

Rationale for introducing Modification 2

In the original protocol, the primary PK parameters listed in Section 7.4.2.2 were not mentioned as primary variables.

List of all CSP sections affected by Modification 2:

- Synopsis
- Section 4.1

Modification 3: Addition of criteria for dose modification of BAY 1163877

Rationale for introducing Modification 3

Criteria for dose modifications of BAY 1163877 for liver toxicity and tissue mineralization were not provided in the original protocol.

List of all CSP sections affected by Modification 3:

- Section 6.4.3

Modification 4: Minor corrections

Rationale for introducing Modification 4

Minor text modifications and corrections of omissions or terminology were done for clarification and to ensure correct and consistent wording.

List of all CSP sections affected by Modification 4:

- List of abbreviations
- Section 6.4.2
- Section 6.7
- Section 7.4.4
- Section 14.2

15.1.2 Changes to the protocol

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment. Deletions are crossed out in the "old text". Additions are underlined in the "new text". Corrections of typing errors, omissions or terminology (minor corrections) are not highlighted in this amendment.

Synopsis

This section was changed as a result of Modifications 1 and 2.

Old text:

Title	**…**
Short title	**…**

Clinical study phase	**…**
Project number	**…**
Study objective(s)	**…**
Test drug(s)	**…**
Name of active ingredient	**…**
Formulation	Ready-to use solution for oral application (10 mg BAY 1163877 per 1 mL solution)
Dose(s)	**…**
Route of administration	**…**
Duration of treatment	Duration and dosing schedule for subjects participating in PK assessments (all subjects of study Part 1 and at least 12 subjects of study Part 2): Subjects will receive BAY 1163877 on a continuous schedule starting with single-dose administration on Cycle 1, Day 1, followed by a "drug-free day" (to enable single dose PK assessments). 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 each Cycle. Duration and dosing schedule for subjects of study Part 2 without PK assessment:
Duration of treatment **(continued)**	Subjects will receive BAY 1163877 twice daily from Cycle 1, Day 1 ongoing. Evidence of tumor progression, **…**
Reference drug (s)	**…**
Indication	**…**

Diagnosis and main criteria for inclusion	**…**
Study design	**…**
Methodology	Eligible cancer subjects will be enrolled at multiple centers in Europe and Asia. In total, the "on study" period for the subjects comprises 3 phases: • Screening (minimum 7 days, maximum 28 days) • Treatment *Study Part 1 / dose escalation + MTD expansion (all comer):* Individual number of 21-day Cycles with BAY 1163877 monotherapy until disease progression or as along as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs Study Part 2 / MTD expansion (sqNSCLC + BC): Individual number of 21-day Cycles with continuous BAY 1163877 monotherapy until disease progression or as along as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs. Note: Treatment with BAY 1163877at MTD**…** **…** **Pharmacokinetics (PK):** Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma on Cycle 1, Day 1 (up to 48 hours after dosing) and on Cycle 1, Day 15 (up to 12 hours after dosing), respectively, in all subjects participating in Study Part 1 (all comer) and at least 12 subjects participating in Study Part 2 (sqNSCLC + BC).

Methodology **(continued)**	Plasma concentration of BAY 1163877**…** **…** **Cardiovascular assessment:** Blood pressure (BP) and heart rate (HR) will be measured at screening, frequently on PK profile days in Cycle 1 ~~(see above)~~ and once at all other visits during treatment and follow up. **Electrocardiogram (ECG):** 12-lead ECG readings will be performed at screening, on Cycle 1, Day 1 ~~(before, 2, 3 and 24 hours after single dosing~~) and ~~Day~~ 15 ~~(before, 2 and 3 hours after dosing~~), and on Day 1 of each subsequent Cycle ~~(once after morning dose)~~. **At screening and in Cycle 1, ECG readings should be done in triplicate.** The triplicate ECGs will be recorded in close sequence and not more than 2 minutes apart. In all subsequent Cycles (Cycle ≥ 2), ECG readings will be performed as single readings. **…**
Type of control	**…**
Number of subjects	Up to 111 subjects will be enrolled in the screening phase of the study. • *Study Part 1 / dose escalation (all comer)*: The total number of subjects will depend on the number of cohorts necessary to identify the MTD. • Study Part 1 / MTD expansion (all comer): **...**
Primary variable	The primary variable for MTD determination will be the incidence of DLTs during the first 21 days of treatment (Cycle 1). The primary study outcome is the MTD being defined as the maximum dose at which the incidence of DLTs during Cycle 1 is below 20%.
Plan for statistical analysis	…The incidence of subjects with DLTs during Cycle 1 will be summarized by cohort and, as possible, modeled as a function of BAY 1163877 dose using Bayesian logistic regression to guide the dose selection.

New text:

Title	…
Short title	…
Clinical study phase	…
Project number	…
Study objective(s)	…
Test drug(s)	…
Test drug(s)	…
Name of active ingredient	…
Formulation IMP 1	Ready-to use solution for oral application (10 mg BAY 1163877 per 1 mL solution)
Formulation IMP 2	Tablet (50 mg tablet and 200 mg tablet)
Dose(s)	…
Route of administration	…
Duration of treatment	Duration and dosing schedule for subjects participating in PK assessments (all subjects of study Part 1 and at least 12 subjects of study Part 2): Subjects will receive BAY 1163877 (tablet or solution) on a continuous schedule starting with single-dose administration on Cycle 1, Day 1, followed by a "drug-free day" (to enable single dose PK assessments). 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 each Cycle. Duration and dosing schedule of subjects enrolled for tablet relative bioavailability assessment ("tablet bridging cohort") of study Part 1:

Duration of treatment (continued)	Subjects will receive a single dose of tablet formulation on Cycle 1, Day -3, and then continue with the solution formulation starting on Cycle 1, Day 1, according to the schedule described above. Duration and dosing schedule for subjects of study Part 2 without PK assessment: Subjects will receive BAY 1163877 (tablet or solution) twice daily from Cycle 1, Day 1 ongoing. Evidence of tumor progression, **…**
Reference drug (s)	**…**
Indication	**…**
Diagnosis and main criteria for inclusion	**…**
Study design	**…**
Methodology	Eligible cancer subjects will be enrolled at multiple centers in Europe and Asia. In total, the "on study" period for the subjects comprises 3 phases: • Screening (minimum 7 days, maximum 28 days) • 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 + BC):* Individual number of 21-day Cycles with continuous BAY 1163877 monotherapy (tablet or solution) until disease progression or as along

Methodology (continued)	as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs. Note: Treatment with BAY 1163877 at MTD **…** **….** **Pharmacokinetics (PK):** Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 (up to 48 hours after dosing) in the "tablet bridging cohort", and on Cycle 1, Day 1 (up to 48 hours after dosing) and on Cycle 1, Day 15 (up to 12 hours after dosing), respectively, in all subjects participating in Study Part 1 (all comer) and in at least 12 subjects participating in Study Part 2 (sqNSCLC + BC). Plasma concentration of BAY 1163877**…** **…** **Cardiovascular assessment:** Blood pressure (BP) and heart rate (HR) will be measured at screening, frequently on PK profile days in Cycle 1, and once at all other visits during treatment and follow up. **Electrocardiogram (ECG):** 12-lead ECG readings will be performed at screening, on Cycle 1, Days -3 and -2 ("tablet bridging cohort" only), on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle, and at the EOT visit. **At screening and in Cycle 1, ECG readings should be done in triplicate.** The triplicate ECGs will be recorded in close sequence and not more than 2 minutes apart. In all subsequent Cycles (Cycle ≥ 2) and at the EOT visit, ECG readings will be performed as single readings. **…**
Type of control	**…**
Number of subjects	Up to 111 subjects will be enrolled in the screening phase of the study. • *Study Part 1 / dose escalation (all comer)*: The total number of subjects will depend on the number of cohorts necessary to identify the MTD.
Number of subjects	Relative bioavailability of the tablet formulation in comparison to the solution formulation will be

(continued)	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)*: **…**
Primary variables	Determination of MTD The primary variable for MTD determination will be the incidence of DLTs during the first 21 days of treatment (Cycle 1). The primary study outcome is the MTD being defined as the maximum dose at which the incidence of DLTs during Cycle 1 is below 20%. Pharmacokinetics: (BAY 1163877) **On Cycle 1 Day -3 ("tablet bridging cohort" only) and Cycle 1, Day 1:** C_{max}, AUC(0-12), AUC(0-t_{last}), AUC and corresponding dose adjusted parameters (C_{max}/D, AUC(0-12)/D AUC(0-t_{last})/D, AUC/D and AUC) **For Cycle 1, Day 15:** $C_{max,md}$, C_{max}/D_{md}, $AUC(0\text{-}12)_{md}$, $AUC(0\text{-}12)/D_{md}$, $AUC(0\text{-}t_{last})_{md}$, and $AUC(0\text{-}t_{last})/D_{md}$.
Plan for statistical analysis	**…** The incidence of subjects with DLTs during Cycle 1 will be summarized by cohort and, as possible, modeled as a function of BAY 1163877 dose using Bayesian logistic regression to guide the dose selection. PK data will be summarized by descriptive statistics. To investigate dose proportionality an ANOVA will be performed on the log-transformed values of appropriate PK parameters and 90% confidence intervals will be derived.

Section 2: Study objectives

This section was changed as a result of Modification 1.

Old text:

Secondary objectives include:

- To evaluate biomarker status, pharmacodynamic (PD) parameters, and tumor response.

New text:

Secondary objectives include:

- 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.

Section 4: Study design

This section was changed as a result of Modification 1.

Old text:

Design overview

…

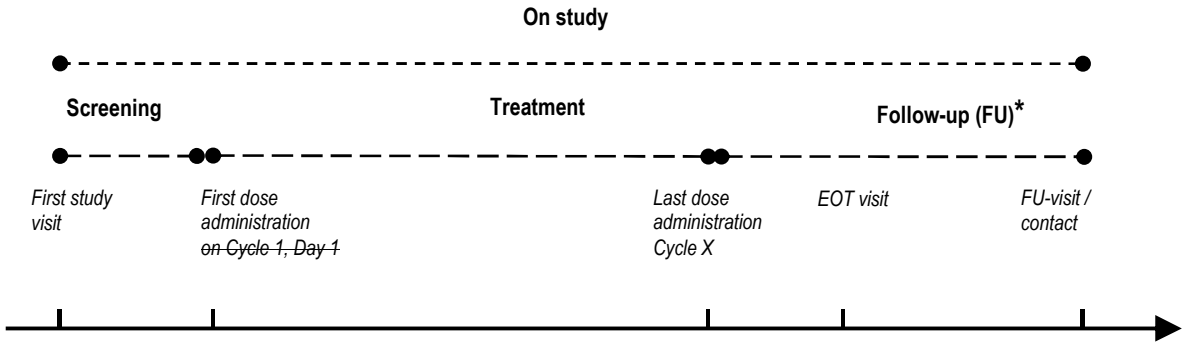
Targeted / planned enrollment:

- *Study Part 1 / dose escalation (all comer)*: The total number of subjects will depend on the number of cohorts necessary to identify the MTD.
- *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 + BC)*: 40 additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC and 20 evaluable subjects with BC treated at MTD.

~~The minimum number of valid subjects completing study treatments, and PK is 3 per cohort.~~ PK assessments will be performed in all subjects participating in study Part 1 / dose escalation and MTD expansion (all comer). Additionally, PK assessments are planned in at least 12 subjects participating in study Part 2 / MTD expansion (sqNSCLC + BC) such that valid PK data are available in 8 subjects.

Study periods:

Figure 4-1: Schematic presentation of the treatment design



*Follow-up:
- EOT (End of Treatment) visit within 7-14 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 4 1):

- Screening (minimum 7 days, maximum 28 days)
- Treatment
  - *Study Part 1 / dose escalation + MTD expansion (all comer)*:
    Individual number of 21-day Cycles with BAY 1163877 monotherapy until disease progression or as along as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.
  - *Study Part 2 / MTD expansion (sqNSCLC +BC)*:
    Individual number of 21-day Cycles with continuous BAY 1163877 monotherapy until disease progression or as along 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") and Part 2 (expansion cohort "sqNSCLC + BC") can run in parallel.
- Follow-up (FU)**….**

…

Treatment: Subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects of study Part 2) will receive BAY 1163877 on a continuous schedule starting with single-dose administration on Cycle 1, Day 1, followed by a "drug-free day" (to enable single dose PK assessments). 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 the maximum tolerated dose is determined.

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

At home, **…**

Pharmacokinetics (PK): Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma on Cycle 1, Day 1 and Day 15~~, respectively,~~ in all subjects participating in Part 1 (all comer) and in at least 12 subjects participating in Part 2 (sqNSCLC + BC).

Plasma concentration of BAY 1163877**…**

Safety / tolerability:

…

Women of childbearing potential must have a negative pregnancy test performed within 7 days prior to first treatment with BAY 1163877 (i.e. 1 week before Cycle 1, Day 1).

…

Electrocardiogram (ECG): 12-lead ECG readings in ~~supine position~~ will be performed at screening, on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle. **At screening and in Cycle 1, ECG readings should be done in triplicate**. The triplicate ECGs will be recorded in close sequence and not more than 2 minutes apart. In all subsequent Cycles (Cycle ≥ 2), ECG readings will be performed as single readings. **…**

New text:

Design overview

...

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.

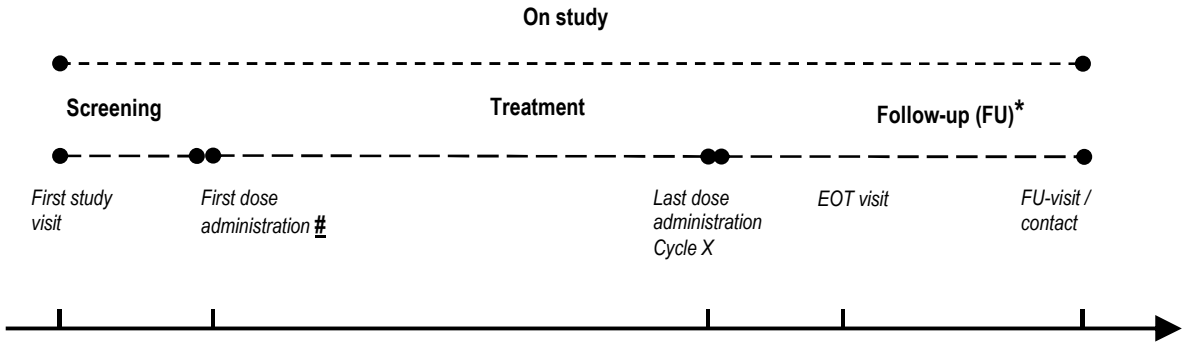
- *Study Part 1 / MTD expansion (all comer)*: Additional subjects will be enrolled to have 20 evaluable "all comer" subjects treated at MTD.

- *Study Part 2 / MTD expansion (sqNSCLC + BC)*: 40 additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC and 20 evaluable 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). Additionally, PK assessments are planned in at least 12 subjects participating in study Part 2 / MTD expansion (sqNSCLC + BC) such that valid PK data are available in 8 subjects.

Study periods:

Figure 4-1: Schematic presentation of the treatment design



The first dose will be administered on Cycle 1, Day 1, except for subjects participating in relative bioavailability assessment who will receive a single dose administered as tablet formulation on Cycle 1, Day -3.

*Follow-up:
- EOT (End of Treatment) visit within 7-14 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 4 1):

- Screening (minimum 7 days, maximum 28 days)
- 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 + BC):*
    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.

  Note: Treatment with BAY 1163877 at MTD in Part 1 (expansion cohort "all comer") and Part 2 (expansion cohort "sqNSCLC + BC") can run in parallel.
- Follow-up (FU)…

…

Treatment: Subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects of study Part 2) will receive BAY 1163877 (tablet or solution) on a continuous schedule starting with single-dose administration on Cycle 1, Day 1, followed by a "drug-free day" (to enable single dose PK assessments). 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 the maximum tolerated dose is determined.

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.

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, **…**

Pharmacokinetics (PK): Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 in the "tablet bridging cohort", and on Cycle 1, Days 1 and 15 in all subjects participating in Part 1 (all comer) and in at least 12 subjects participating in Part 2 (sqNSCLC + BC).

Plasma concentration of BAY 1163877 **…**

Safety / tolerability:

…

Women of childbearing potential must have a negative pregnancy test performed within 7 days prior to first treatment with BAY 1163877 (i.e. 1 week before Cycle 1, Day 1 or Cycle 1, Day -3, if applicable).

…

Electrocardiogram (ECG): 12-lead ECG readings will be performed at screening, on Cycle 1, Day -3 ("tablet bridging cohort" only), on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle, and at the EOT visit. **At screening and in Cycle 1, ECG readings should be done in triplicate**. The triplicate ECGs will be recorded in close sequence and not more than 2 minutes apart. In all subsequent Cycles (Cycle ≥ 2) and at the EOT visit, ECG readings will be performed as single readings. **…**

Section 4.1: Primary variable(s)

This section was changed as a result of Modification 2.

Old text:

This is primarily a descriptive safety and tolerability Phase I study. The primary variable for MTD determination will be the incidence of DLTs during the first 21 days of treatment (Cycle 1). The primary study outcome is the MTD being defined as the maximum dose at which the incidence of DLTs during Cycle 1 is below 20%.

New text:

This is primarily a descriptive safety and tolerability Phase I study. The primary variable for MTD determination will be the incidence of DLTs during the first 21 days of treatment (Cycle 1). The primary study outcome is the MTD being defined as the maximum dose at which the incidence of DLTs during Cycle 1 is below 20%.

Primary PK parameters are provided in Section 9.4.2.2.

Section 6.1: Treatments to be administered

This section was changed as a result of Modification 1.

Old text:

Investigational medicinal product (IMP) – test drug

- BAY 1163877 drinking solution (test drug)

Non-investigational product(s) (NIMP)

Not applicable

In study Part 1 / dose escalation + MTD expansion (all comer), **…**

…. The dose decision will be guided by model-based dose-response analysis of the DLT rates (see Section 14.4).

~~A solid (tablet) formulation is planned for later cohorts. The switch from liquid to solid formulation is planned after relative bioavailability assessment.~~

In study Part 2 / MTD expansion (sqNSCLC +BC), **…**

New text:

Investigational medicinal product (IMP) – test drug

- BAY 1163877 drinking solution (test drug)
- BAY 1163877 tablet (test drug)

Non-investigational product(s) (NIMP)

Not applicable

In study Part 1 / dose escalation + MTD expansion (all comer), **…**

… The dose decision will be guided by model-based dose-response analysis of the DLT rates (see Section 16.4).

In the “tablet bridging cohort”, relative bioavailability of the tablet formulation in comparison to the solution formulation will be assessed by administration of a single dose

of the tablet formulation on Cycle 1, Day -3 in at least 3 subjects. Starting with Cycle 1, Day 1, subjects enrolled in this cohort will continue with the solution formulation as described above.

In study Part 2 / MTD expansion (sqNSCLC +BC), **…**

Section 6.2: Identity of study treatment

This section was changed as a result of Modification 1.

Old text:

The details of BAY 1163877 are given in Table 6-1.

Table 6-1: Identity of test drug (IMP): BAY 1163877 ~~liquid~~ formulation

Generic name / brand name / INN	**…**
Substance code number(s)	**…**
Development no. / SH no.	BAY1163877 HCl H2O SOL 1% 11 mL ORAL
Galenical form / formulation / vehicle and reconstitution, if applicable	**…**
Composition	**…**
Strength (amount of drug per unit) or concentration	**…**
Type of packaging and content	**…**
Marketing Authorization Holder if applicable	**…**

Labeling: **…**

New text:

The details of the two formulations of BAY 1163877 planned to be used in this study are given in Table 8-1(solution) and Table 8-2(tablet).

Table 6-1: Identity of test drug (IMP): BAY 1163877 solution formulation

Generic name / brand name / INN	…
Substance code number(s)	…
Material / formulation) number(s)	BAY1163877 HCl H2O SOL 1% 11 mL ORAL
Galenical form / formulation / vehicle and reconstitution, if applicable	…
Composition	…
Strength (amount of drug per unit) or concentration	…
Type of packaging and content	…
Marketing Authorization Holder if applicable	…

Table 6-2: Identity of test drug (IMP): BAY 1163877 tablet formulation

Generic name / brand name / INN	Not applicable
Substance code number(s)	BAY 1163877 as BAY 1213802
Material / formulation) number(s)	**81820457 for** BAY 1163877 HCL TAB 50.0 mg 363 COAT **81820449 for** BAY 1163877 HCL TAB 200.0 mg 364 COAT
Galenical form / formulation / vehicle and reconstitution, if applicable	IR (immediate release) tablets
Composition	Active ingredients: BAY 1163877 as hydrochloride Other ingredients: Cellulose microcrystalline (filler) Lactose monohydrate (filler) Crospovidone (disintegrant) Copovidone (binder) Magnesium stearate (lubricant) Silica colloidal anhydrous (glidant) Lacquer red (coating material)* * (contains hypromellose, macrogol, titanium dioxide,ferric oxide red)
Strength (amount of drug per unit) or concentration	50 mg BAY 1163877 per tablet 200 mg BAY 1163877 per tablet
Type of packaging and content	HDPE bottles with screw cap closure
Marketing Authorization Holder if applicable	Not applicable

Labeling: **...**

Section 6.4.2.1: Dosing schedule

This section was changed as a result of Modification 1.

Old text:

BAY 1163877 will be given in cycles. Each cycle lasts 21 days. There will be no break between treatment cycles.

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

Cycle 1:	Single-dose administration of BAY 1163877 on Cycle 1, Day 1 (in the morning) No administration of BAY 1163877 on Cycle 1, Day 2 ("drug-free day") Twice daily administration of BAY 1163877 on Days 3-21
Cycle 2 and subsequent cycles:	Twice daily administration of BAY 1163877 on Days 1-21.

*Study Part 2 / dose expansion (sqNSCLC + BC):***…**

…

New text:

BAY 1163877 will be given in cycles. Each cycle lasts 21 days. There will be no break between treatment cycles.

Subjects will receive either the solution (IMP 1) or the tablet (IMP 2) formulation of BAY 1163877, except for subjects in the "tablet bridging cohort" who will receive both a single dose using the tablet formulation and multiple doses using the solution formulation.

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

Cycle 1 Day -3 ("tablet bridging cohort" only):	Single-dose administration of BAY 1163877 tablet formulation on Cycle 1, Day -3; thereafter continuation with solution formulation starting on Cycle 1, Day 1 (see dosing schedule below)
Cycle 1:	Single-dose administration of BAY 1163877 on Cycle 1, Day 1 (in the morning) No administration of BAY 1163877 on Cycle 1, Day 2 ("drug-free day") Twice daily administration of BAY 1163877 on Days 3-21
Cycle 2 and subsequent cycles:	Twice daily administration of BAY 1163877 on Days 1-21.

Study Part 2 / dose expansion (sqNSCLC + BC): **…**

…

Section 6.4.2.2: Mode of administration

This section was changed as a result of Modification 1.

Old text:

BAY 1163877 will be administered per os (p.o.) at least 1 hour before or 2 hours after a meal or snack.

Subjects should not take additional doses of BAY 1163877 to compensate for a missed dose.

New text:

BAY 1163877 will be administered per os (p.o.) at least 1 hour before or 2 hours after a meal or snack.

The ready-to-use solution will be administered directly and undiluted via disposable syringe into the mouth of the subject. Immediately after administration, the subject has to drink a glass of water (approximately 200 mL / 7 ounces).

BAY 1163877 tablets should be taken with a glass of water (approximately 200 mL / 7 ounces). Tablets should be swallowed intact and not chewed.

Subjects should not take additional doses of BAY 1163877 to compensate for a missed dose.

Section 6.4.2.3: Treatment duration

This section was changed as a result of Modification 1.

Old text:

BAY 1163877 will be administered on a continuous schedule in at least one 21-day Cycle with no break between cycles until progression or as along as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.

Treatment starts on Cycle 1, Day 1.

Further details on dosing schedule are provided in Section 6.4.2.1.

New text:

BAY 1163877 will be administered on a continuous schedule in at least one 21-day Cycle with no break between cycles until progression or as along as clinical benefit is assumed by the investigator or until unacceptable toxicity occurs.

For subjects in the “tablet bridging cohort”, treatment starts on Cycle 1, Day -3.

For all other subjects, treatment starts on Cycle 1, Day 1.

Further details on dosing schedule are provided in Section 8.4.2.1.

Section 6.4.3: Dose modification and delays

This section was changed as a result of Modification 3.

Old text:

Doses of study drug (BAY 1163877) may be delayed or reduced in case of clinically significant hematologic and other toxicities that are possibly, probably or definitely related to study drug therapy. Toxicities will be graded using the CTCAE v 4.03 (see Section 14.5).

No intra-subject dose escalation will be permitted. However, the dose can be reduced or delayed for an individual subject based on toxicities that are related to study drug.

If a subject experiences a DLT during Cycle 1, the next dose of BAY 1163877 can be delayed for up to 21 days, but only in cases ~~where~~ Grade 3 ~~events occur~~ no longer than 7 days.

All subjects who are re-treated following a DLT should undergo dose reduction (see Table 6-3).

If the toxicity resolves to ≤ Grade 1, the next ~~dose~~ of BAY 1163877 can be considered. ~~Re-treatment for this subject should be at 1 dose level below the initial dose~~ (see Table 6-3), provided that this dose level has been evaluated during the dose escalation part of the study. Detailed dose adjustments for hematological toxicities are described in Table 6-4. If the subject was dosed at the starting dose level, the subject should be removed from the study. If the toxicity fails to resolve to ≤ Grade 1within 21 days after the planned treatment date, the subject ~~should~~ be removed from the study. Subjects who experience a Grade 4 non-hematological toxicity ~~should~~ be removed from the study.

Drug-related adverse events of ≥ Grade 3

For ≥ Grade 3 adverse event regarded as related to study drug, the ~~dose~~ of BAY 1163877 can be delayed for up to 21 days. If the toxicity fails to resolve to ≤ Grade 1 within 21 days after the ~~planned~~ dosing date, the subject ~~should~~ be removed from the study. If the toxicity resolves to ≤ Grade 1, the next ~~dose~~ of BAY 1163877 can be considered. ~~Re-treatment for this subject should be reduced by 1 dose level. Detailed d~~dose adjustments for toxicities are described in Table 6-2.

If the re-treatment reproduces the same toxicity grade, the next ~~dose~~ of BAY 1163877 can be delayed for up to 21 days until the toxicity has resolved to ≤ Grade 1. Re-treatment is possible at 1 dose level below.

Subjects who experience a Grade 4 non-hematological toxicity ~~should~~ be removed from the study. If more than 2 dose reductions are required, treatment will be discontinued.

Table 6-2: Scheme for dose-level reduction of BAY 1163877 in subjects with solid tumors

Dose level	Action
-1	1 dose below level of DLT occurrence[a]
-2	2 doses below level of DLT occurence[a]
-3	Discontinue study drug permanently

a alternatively, treatment can be continued at an interim dose level with at least 3 subjects evaluated

Table 6-3: Hematological criteria for dose delay and dose modification

Grade[a]	ANC (10^9/L)	Platelets (10^9/L)	Dose delay	Dose modification
1 - 2	≥1.0	≥50	Treat ~~on time~~	No change
3	<1.0 - 0.5	<50 - 25	Delay[b] until ≤ Grade 1	Decrease 1 dose level[c]
4	<0.5	<25	Delay[b] until ≤ Grade 1	Decrease 1 dose level[c]

a Applies to all kinds of hematological toxicities; ANC and platelet count displayed as examples.
b If no recovery after 21 days delay, treatment will be discontinued.
c Dose will not be re-escalated to original dose level after reduction for toxicity. If more than 2 dose reductions are required, treatment will be discontinued.

Table 6-4: Non-hematological criteria for dose delay and dose modification

Grade[a]	Dose delay	Dose modification
1 – 2	Treat ~~on time~~	No change
3	Delay[b] until ≤ Grade 1	Decrease 1 dose level[c]
4	Discontinue study drug permanently	Discontinue study drug permanently

a Excludes alopecia. A maximum duration of 48 hours of Grade 3 nausea or vomiting will be allowed and not be considered DLT.
b If no recovery after 21 days delay, treatment will be discontinued.
c Dose will not be re-escalated after reduction for toxicity. If more than 2 dose reductions are required, treatment will be discontinued.

New text:

Doses of study drug (BAY 1163877) may be delayed or reduced in case of clinically significant hematologic and other toxicities that are possibly, probably or definitely related to study drug therapy. Toxicities will be graded using the CTCAE v 4.03 (see Section 14.5).

No intra-subject dose escalation will be permitted. However, the dose can be reduced or delayed for an individual subject based on toxicities that are related to study drug.

If a subject experiences a DLT during Cycle 1, the next dose of BAY 1163877 can be delayed for up to 21 days, but only in cases Grade 3 non-hematological toxicities persist no longer than 7 days.

All subjects who are re-treated following a DLT should undergo dose reduction (see Table 6-3).

If the toxicity resolves to ≤ Grade 1, the next dosing of BAY 1163877 at 1 dose level below the current dose (see Table 6-3) can be considered, provided that this dose level has been evaluated during the dose escalation part of the study. Detailed dose adjustments for hematological toxicities are described in Table 6-4. If the subject was dosed at the starting dose level, the subject should be removed from the study. If the toxicity fails to resolve to ≤ Grade 1within 21 days after the planned treatment date, the subject will be removed from the study. Subjects who experience a Grade 4 non-hematological toxicity will be removed from the study.

Drug-related adverse events of ≥ Grade 3

For ≥ Grade 3 adverse event regarded as related to study drug, the next dosing of BAY 1163877 can be delayed for up to 21 days. If the toxicity fails to resolve to ≤ Grade 1 within 21 days after the scheduled dosing date, the subject will be removed from the study. If the toxicity resolves to ≤ Grade 1, the next dosing of BAY 1163877 at 1 dose level below the current dose (see Table 6-3) can be considered, provided that this dose level has been evaluated during the dose escalation part of the study. Dose adjustments for toxicities are detailed in Table 6-3.

If the re-treatment reproduces the same toxicity grade, the next dosing of BAY 1163877 can be delayed for up to 21 days until the toxicity has resolved to ≤ Grade 1. Re-treatment is possible at 1 dose level below the previous dose.

Subjects who experience a Grade 4 non-hematological toxicity will be removed from the study. If more than 2 dose reductions are required, treatment will be permanently discontinued.

Table 6-3: Scheme for dose-level reduction of BAY 1163877 in subjects with solid tumors

Dose level	Action
-1	1 dose below level of DLT occurrence[a]
-2	2 doses below level of DLT occurence[a]
-3	Discontinue study drug permanently

a alternatively, treatment can be continued at an interim dose level with at least 3 subjects evaluated

Table 6-4: Hematological criteria for dose delay and dose modification

Grade[a]	ANC (10^9/L)	Platelets (10^9/L)	Dose delay	Dose modification
1 - 2	≥1.0	≥50	Treat as scheduled	No change
3	<1.0 - 0.5	<50 - 25	Delay[b] until ≤ Grade 1	Decrease 1 dose level[c]
4	<0.5	<25	Delay[b] until ≤ Grade 1	Decrease 1 dose level[c]

a Applies to all kinds of hematological toxicities; ANC and platelet count displayed as examples.
b If no recovery after 21 days delay, treatment will be permanently discontinued.
c Dose will not be re-escalated to original dose level after reduction for toxicity. If more than 2 dose reductions are required, treatment will be discontinued.

Table 6-5: Non-hematological criteria for dose delay and dose modification

Grade[a]	Dose delay	Dose modification
1 – 2	Treat as scheduled	No change
3	Delay[b] until ≤ Grade 1	Decrease 1 dose level[c]
4	Discontinue study drug permanently	Discontinue study drug permanently

a Excludes alopecia. A maximum duration of 48 hours of Grade 3 nausea or vomiting will be allowed and not be considered DLT.
b If no recovery after 21 days delay, treatment will be permanently discontinued.
c Dose will not be re-escalated after dose reduction for toxicity. If more than 2 dose reductions are required, treatment will be permanently discontinued.

Liver toxicity - amended

Dose modifications of BAY 1163877 for liver toxicity are presented in Table 6-6. Liver toxicity refers to ALT and / or AST and / or bilirubin increases and / or hepatic failure considered possibly related to BAY 1163877, and graded according to CTCAE v4.03.

Table 6-6: Dose modifications of BAY 1163877 for liver toxicity

Toxicity	Modification schedule
Grade 1-2	No modifications. Treat as scheduled and check AST, ALT and bilirubin weekly for at least 4 weeks.
Grade 3	Hold BAY 1163877 until recovery to ≤ grade 2 or baseline, then reduce 1 dose level and check AST, ALT and bilirubin weekly for at least 4 weeks.[a]
- 1st reappearance	Hold BAY 1163877 until recovery to ≤ grade 2 or baseline, then reduce 1 additional dose level and check AST, ALT and bilirubin weekly for at least 4 weeks[a].
- 2nd reappearance	Withdraw subject from the study treatment.[b]
Grade 3 with ALT or AST > 8x ULN and a concomitant rise in bilirubin (of any degree compared to previous bilirubin level) or hepatic failure (of any degree)	In case of a negative risk-benefit assessment, consider permanent discontinuation at the first occurrence[b,c] OR Hold BAY 1163877 until recovery to ≤ grade 2 or baseline, then reduce 1 dose level and check AST, ALT and bilirubin weekly for at least 4 weeks[a].
-1st reappearance	Withdraw subject from study treatment.[b]
Grade 4 [b]	Withdraw subject from study treatment.[b]

a If all values remain stable for 2 cycles, dose re-escalation may be considered at the discretion of the investigator. After re-escalation, AST, ALT, and bilirubin should be checked weekly for at least 4 weeks.

b In case of discontinuation, check AST, ALT, and bilirubin weekly until recovery to baseline or stabilization.

c Subjects with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and / or AST.

Tissue mineralization – amended

Dose modifications of BAY 1163877 for tissue mineralization are presented in Table 6-7. Tissue mineralization refers to Ca x PO4 ≥ 70 mg^2/dL^2 considered possibly related to BAY 1163877.

Table 6-7: Dose modifications of BAY 1163877 for tissue mineralization

Toxicity	Modification schedule
Ca x PO4 (≥ 70 mg²/dL²)	Hold BAY 1163877, treat with phosphate chelators until recovery, to Ca x PO4 < 70 mg²/dL². Resume same dose level, continue phosphate chelators and check weekly for at least 4 weeks.
- 1st reappearance	Hold BAY 1163877, treat with phosphate chelators until recovery to Ca x PO4 < 70 mg²/dL², then reduce 1 dose level, continue phosphate chelator and check weekly for at least 4 weeks.
- 2nd reappearance	Hold BAY 1163877 until recovery to Ca x PO4 < 70 mg²/dL², then reduce 1 additional dose level, continue phosphate chelators and check weekly for at least 4 weeks.
- 3rd reappearance	Withdraw subject from study treatment.

Section 7.1.2.3: Treatment

This section was changed as a result of Modification 1.

Old text:

The treatment phase comprises Cycle 1 (21 days) and a variable number of subsequent Cycles (each of 21 days duration) with no break between Cycles.

There will be both visits and possible overnight stays at the study site.

New text:

For subjects in the "tablet bridging cohort", the treatment phase starts on Cycle 1, Day -3, followed by Cycle 1 (21 days) and a variable number of subsequent Cycles (each of 21 days duration) with no break between Cycles.

For all other subjects, the treatment phase comprises Cycle 1 (21 days) and a variable number of subsequent Cycles (each of 21 days duration) with no break between Cycles.

There will be both visits and possible overnight stays at the study site.

Section 7.1.2.3.1: Cycle 1

This section was changed as a result of Modification 1.

Old text:

Days 1-3 (possible overnight stay)

Day 1

- …
- Triplicate 12-lead ECG readings (see Section 7.5.3.4)
- …

New text:

For "tablet bridging cohort" cohort only:

Day -3 to Day -1 (possible overnight stay)

Day -3

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature and body weight
- Triplicate 12-lead ECG readings (see Section 7.5.3.4).
- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Table 14-4
- Calculation of eGFR (see Section 14.9)
- Single oral administration of BAY 1163877 tablet formulation
- PK sampling
- Toxicities / AE assessment and recording (if applicable)

Day -2

- No administration of BAY 1163877 ("drug-free day")
- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature
- Triplicate ECG readings (see Section 7.5.3.4)
- ECOG performance status
- PK sampling

- Toxicities / AE assessment and recording (if applicable)

Day -1

- No administration of BAY 1163877 ("drug-free day")
- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature
- ECOG performance status
- PK sampling
- Toxicities / AE assessment and recording (if applicable)

Days 1-3 (possible overnight stay)

Day 1

- …
- Measurement of body temperature and body weight (measurement of weight not required for subjects in the "tablet bridging cohort")
- …

Section 7.4.1.1: Cardiovascular assessment

This section was changed as a result of Modification 1.

Old text:

...

BP and HR will be measured at the following time points:

- Screening (one measurement within 7 days before start of treatment)
- Cycle 1, Day 1 and Day 2
  - before and 0.5, 1, 2, 3, 4, 6, 8, 12 (Day 1), and 24 (Day 2) hour(s) after single dose administration
- Cycle 1, Day 3

  before and 1, and 2 hour(s) after morning dose
- Cycle 1, Day 15

- before and 0.5, 1, 2, 3, 4, 6, 8 and 12 hour(s) after morning dose [12-hour measurement before evening dose]

…

New text:

…

BP and HR will be measured at the following time points:

- Screening (one measurement within 7 days before start of treatment)
- Cycle 1, Day -3 to Day -1 ("tablet bridging cohort" only)

  before and 0.5, 1, 2, 3, 4, 6, 8, 12 (Day -3), 24 (Day -2) and 48 (Day -1) hour(s) after single-dose administration
- Cycle 1, Day 1 and Day 2

  before and 0.5, 1, 2, 3, 4, 6, 8, 12 (Day 1), and 24 (Day 2) hour(s) after single-dose administration
- Cycle 1, Day 3

  before and 1, and 2 hour(s) after morning dose
- Cycle 1, Day 8 (one measurement)
- Cycle 1, Day 15
  - before and 0.5, 1, 2, 3, 4, 6, 8 and 12 hour(s) after morning dose [12-hour measurement before evening dose]

…

Section 7.4.2.1: Drug measurements

This section was changed as a result of Modification 1.

Old text:

Pharmacokinetics of BAY 1163877 will be evaluated on Cycle 1, Day 1 after single-dose administration and on Cycle 1, Day 15 after multiple-dose administration of BAY 1163877 at the respective dose level achieved during dose escalation.

…

Blood (plasma) samples for PK assessment of **BAY 1163877** will be collected at the following time points:

- Cycle 1, Day 1: <u>single-dose PK</u>

…

New text:

Pharmacokinetics of BAY 1163877 will be evaluated on Cycle 1, Day -3 ("tablet bridging cohort" only), Cycle 1, Day 1 after single-dose administration, and on Cycle 1, Day 15 after multiple-dose administration of BAY 1163877 at the respective dose level achieved during dose escalation.

...

Blood (plasma) samples for PK assessment of **BAY 1163877** will be collected at the following time points:

- Cycle 1, Day -3 ("tablet bridging cohort" only): single-dose PK
  - pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hour(s) post-dose
- Cycle 1, Day 1: single-dose PK

…

Section 7.4.2.2: Pharmacokinetic evaluation

This section was changed as a result of Modification 1.

Old text:

…

Primary PK parameters (plasma): **BAY 1163877**

- **Cycle 1, Day 1 single dose:** C_{max}, C_{max}/D, AUC(0-12), AUC(0-12)/D, AUC(0-t_{last}), AUC(0-t_{last})/D, AUC, and AUC/D
AUC may not be calculated if it is not possible to estimate half-life.
- **Cycle 1, Day 15 multiple dose:** $C_{max,md}$, C_{max}/D_{md}, $AUC(0\text{-}12)_{md}$, $AUC(0\text{-}12)/D_{md}$, $AUC(0\text{-}t_{last})_{md}$, and $AUC(0\text{-}t_{last})/D_{md}$.

Secondary PK parameters (plasma): **BAY 1163877**

- t_{max}, t_{last}, $t_{1/2}$ of Cycle 1, Day 1 and $t_{max,md}$ and $t_{last,md}$ of Cycle 1, Day 15.

Other PK parameters (plasma): **BAY 1163877**

...

New text:

…

Primary PK parameters (plasma): **BAY 1163877**

- **Cycle 1, Day -3 ("tablet bridging cohort" only) and Cycle 1, Day 1 single dose:**
C_{max}, C_{max}/D, AUC(0-12), AUC(0-12)/D, AUC(0-t_{last}), AUC(0-t_{last})/D, AUC, and AUC/D
AUC may not be calculated if it is not possible to estimate half-life.

- **Cycle 1, Day 15 multiple dose:** $C_{max,md}$, C_{max}/D_{md}, $AUC(0\text{-}12)_{md}$, $AUC(0\text{-}12)/D_{md}$, $AUC(0\text{-}t_{last})_{md}$, and $AUC(0\text{-}t_{last})/D_{md}$.

Secondary PK parameters (plasma): **BAY 1163877**

- t_{max}, t_{last}, $t_{1/2}$ of Cycle 1, Day -3 ("tablet bridging cohort" only) and Cycle 1, Day 1 and $t_{max,md}$ and $t_{last,md}$ of Cycle 1, Day 15.

Other PK parameters (plasma): **BAY 1163877**

…

Section 7.5.3.4: Electrocardiogram (ECG)

This section was changed as a result of Modification 1.

Old text:

...

12-lead ECG readings will be performed in the supine position at the following time points:

- Screening (triplicate ECG readings)
- Cycle 1, Day 1 and Day 2 (triplicate ECG readings)
  - before and 2, 3 (Day 1) and 24 (Day 2) hours after single-dose administration
- Cycle 1, Day 15 (triplicate ECG readings) **…**
  - before morning dose, and 2 and 3 hours thereafter
- Cycle ≥ 2, Day 1 (single ECG readings)
  - after morning dose

…

New text:

…

12-lead ECG readings will be performed in the supine position at the following time points:

- Screening (triplicate ECG readings)
- Cycle 1, Day -3 and Day -2 (triplicate ECG readings) ["tablet bridging cohort" only]

  before and 2, 3 (Day -3) and 24 (Day -2) hours after single-dose administration
- Cycle 1, Day 1 and Day 2 (triplicate ECG readings)
  - before and 2, 3 (Day 1) and 24 (Day 2) hours after single-dose administration

- Cycle 1, Day 15 (triplicate ECG readings)
  before morning dose, and 2 and 3 hours thereafter
- Cycle ≥ 2, Day 1 (single ECG readings)
  after morning dose
- EOT visit (single ECG reading)

…

Section 8.2: Analysis sets

This section was changed as a result of Modification 1.

Old text:

…

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

New text:

…

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

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.

Section 8.4.5: Pharmacokinetic data

This section was changed as a result of Modification 1.

Old text:

…

To investigate dose proportionality, an explorative analysis of variance (ANOVA), including the factor cohort, will be performed on the log-transformed values of appropriate PK parameters calculated from single (where applicable) and multiple dose PK profiles.

New text:

…

To investigate dose proportionality, an explorative analysis of variance (ANOVA), including the factor cohort, will be performed on the log-transformed values of

appropriate PK parameters calculated from single (where applicable) and multiple dose PK profiles.

In order to evaluate the relative bioavailability of the tablet formulation, tablet C_{max}/D, $AUC(0\text{-}t_{last})/D$ and AUC/D on Cycle 1, Day -3 will be compared to solution C_{max}/D, $AUC(0\text{-}t_{last})/D$, 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, $AUC(0\text{-}t_{last})/D$, AUC/D will be calculated by retransformation of the logarithmic data using the intra-individual standard deviation of the ANOVA.

Section 14.1: Study flow chart

A flow chart for Cycle 1 Day -3 to Day -1 was added for the "tablet bridging cohort" as a result of Modification 1.

Old text:

Table 14-1 and Table 14-2 in the following provide flow charts presenting the time points for the study related measures / actions.

Table 14-1: Study flow chart: Screening – Study Part 1 and Part 2

Measures / actions	Screening	
	Within 28 Days* before first study drug administration	Within 7 Days* before first study drug administration
…	…	
…		

Table 14–2: Study flow chart: Treatment and Follow-up – Study Part 1 and Part 2

Measures / actions	TREATMENT									FOLLOW-UP
	Cycle 1 (21 days)					Cycle≥2 (21 days)			EOT Visit Within 7-14 days after last dose	FU-Visit / Phone Call[(A)] At 30-35 days after last dose
Day (D)	D1	D2	D3	D8 ±1	D15	D1	D8 ±1	D15 ±1		
…										
…										
Obtain tumor biopsy for biomarker tests[(H)]						**X**				
…										

…

(C) Cardiovascular assessment: Blood pressure (BP) and heart rate (HR) will be measured as follows (see Section 7.4.1.1):

- Cycle 1, Day 1 and Day 2:
  - before and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 (Day 2) hour(s) after single-dose administration
- Cycle 1, Day 3:
  - before and 1 and 2 hour(s) after morning dose
- Cycle 1, Day 15:
  - before and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 (Day 2) hour(s) after single-dose administration

Cycle ≥ 2 ~~and follow up~~……
each visit (one measurement)…
Follow up **…**

(D) In Cycle 1, all 12-lead ECGs should be performed in triplicate in close sequence and **not more than 2 minutes apart**. ECG readings will be performed at the following time points:

Cycle 1, Day 1 and Day 2 (triplicate ECG readings): before and 2, 3 (Day 1) and 24 (Day 2) hours after single-dose administration

Cycle 1, Day 15 (triplicate ECG readings): before morning dose, and 2 and 3 hours thereafter

Cycle ≥ 2, Day 1 (single ECG reading): after morning dose

…

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

New text:

Table 14-1, Table 14-2 and Table 14-3 in the following provide flow charts presenting the time points for the study related measures / actions.

Table 14-1: Study flow chart: Screening – Study Part 1 and Part 2

Measures / actions	Screening	
	Within 28 Days* before first study drug administration	Within 7 Days* before first study drug administration
…	…	
…		

Table 14 2: Study flow chart: Treatment (Cycle 1, Day -3 to Day -1 – Study Part 1

Measures / actions	**TREATMENT (only for "tablet bridging cohort")**		
	Cycle 1		
	Day -3	Day -2	Day -1
Concomitant medication	**X**	**X**	**X**
Physical examination	**X**	**X**	**X**
Ask subject for changes in vision(A)	**X**	**X**	**X**
Cardiovascular assessment(B)	**X→ → X**		**X**
Body temperature	**X**	**X**	**X**
Body weight	**X**		
12-lead ECG readings(C)	**X**	**X**	
ECOG performance status	**X**	**X**	**X**
Blood / urine collection for safety lab tests(D)	**X**		
Calculation of eGFR(E)	**X**		
PK blood sampling(F)	**X→ → X**		
Administration of BAY 1163877 tablet (single dose)(G)	**X**		
Toxicities / AE assessment	**X**	**X**	**X**

(A) If change in vision is reported by subject an ophthalmological examination must be performed (see Section 7.5.3.2)

(B) Cardiovascular assessment: Blood pressure (BP) and heart rate (HR) will be measured as follows (see Section 7.4.1.1): before and 0.5, 1, 2, 3, 4, 6, 8, 12 (Day -3), 24 (Day -2) and 48 (Day -1) hour(s) after single-dose administration

If a reduction of systolic BP below 90 mmHg or an increase in HR to more than 120 bpm is detected, the assessment has to be repeated after 2 hours. When blood pressure measurement and PK sample collection are scheduled at the same time point, subject's blood pressure will be measured before collection of the PK sample.

(C) 12-lead ECGs should be performed in triplicate in close sequence and **not more than 2 minutes apart**. ECG readings will be performed at the following time points:
before and 2, 3 (Day -3) and 24 (Day -2) hours after single-dose administration

(D) Safety laboratory tests, see Table 14–4

(E) For calculation of eGFR (estimated glomerular filtration rate), see Section 14.9

(F) PK sampling will be done as follows (for details see Laboratory Manual):•
- pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12 (Day -3), 24 (Day -2) and 48 (Day -1) hour(s) after single-dose administration[

(G) Oral administration of BAY 1163877 tablet formulation on Cycle 1, Day -3 will be done by a member of the site.

Table 14-3: Study flow chart: Treatment (Cycle ≥1) and Follow-up – Study Part 1 and Part 2

Measures / actions	TREATMENT									FOLLOW-UP
	Cycle 1 (21 days)					Cycle≥2 (21 days)			EOT Visit Within 7-14 days after last dose	FU-Visit / Phone Call[A] At 30-35 days after last dose
Day (D)	D1	D2	D3	D8 ±1	D15	D1	D8 ±1	D15 ±1		
…										
…										
Obtain tumor biopsy for biomarker tests[H]						X (Cycle 2 only)				
…										

…

(C) Cardiovascular assessment: Blood pressure (BP) and heart rate (HR) will be measured as follows (see Section 7.4.1.1):

- Cycle 1, Day 1 and Day 2: before and 0.5, 1, 2, 3, 4, 6, 8, 12 (Day 1), and 24 (Day 2) hour(s) after single-dose administration
- Cycle 1, Day 3: before and 1 and 2 hour(s) after morning dose
- Cycle 1, Day 8: (one measurement)
- Cycle 1, Day 15: before and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 (Day 2) hour(s) after single-dose administration
- Cycle ≥ 2: each visit (one measurement)…

Follow up …

(D) In Cycle 1, all 12-lead ECGs should be performed in triplicate in close sequence and **not more than 2 minutes apart**. ECG readings will be performed at the following time points:

Cycle 1, Day 1 and Day 2 (triplicate ECG readings): before and 2, 3 (Day 1) and 24 (Day 2) hours after single-dose administration

Cycle 1, Day 15 (triplicate ECG readings): before morning dose, and 2 and 3 hours thereafter

Cycle ≥ 2, Day 1 (single ECG reading): after morning dose

EOT visit (single ECG reading)

…

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

Section 14.2: Laboratory examinations

This section was changed as a result of Modifications 1 and 3. A missing link to Table 14-6 was added.

Old text:

Table 14-3, Table 14-4 and Table 14-6 provide the parameters and time points for the laboratory examinations (safety laboratory tests, biomarker investigations) to be performed during the study. Instructions for biomarker and PK sample collection, processing, storage and shipment will be described in a separate document (e.g. lab manual).

Table 14-3: Parameters and time points of laboratory examinations performed at local laboratory or study site (safety laboratory) – Study Part 1 and Part 2

Parameters	Screen-ing	Treatment Each Cycle			Follow-up	
		Day 1	Day 8	Day 15	EOT visit	FU visit
BLOOD						
Hematology: …	X	X	X	X	X	X
Coagulation: PT or PT-INR and PTT(A)	X	X	X	X	X	X
Biochemistry: Biochemistry: AST / GOT, ALT / GPT, gamma-GT, AP, LDH, amylase, lipase, glucose, triglycerides, creatinine(B), BUN, uric acid, bilirubin (total & direct), total protein, albumin, sodium, potassium, chloride, CPK,	X	X	X	X	X	X
Virology: …	X					
URINE						
Macroanalysis:	X	X	X	X	X	X
Urinalysis (dip stick): pH, ~~erythrocytes or hemoglobin~~ (blood, protein, glucose, bilirubin, urobilinogen, ketone, nitrite, leucocytes (or leucocyte esterase), specific gravity	X	X	X	X	X	X
Laboratory analysis(C): …	X	X	X	X	X	X
Microscopic urinalysis(D): …	X	X	X	X	X	X
Pregnancy test(F)	X					

(A) **…**
(B) **…**
(C) **…**
(D) **…**
(F) **…**

ALT / GPT = alanine aminotransferase / glutamic pyruvic transaminase
anti-HCV = hepatitis C virus antibodies
anti-HIV 1+2 = human immune deficiency virus 1 and 2 antibodies
AP = alkaline phosphatase
AST / GOT = aspartate aminotransferase / glutamic oxaloacetic transaminase
BUN = blood urea nitrogen
CPK = creatine phosphokinase
CRP = C-reactive protein
gamma GT = gamma glutamyl transferase
HBsAg = hepatitis B virus surface antigen
MCH = mean corpuscular hemoglobin
MCHC = mean corpuscular hemoglobin concentration
MCV = mean corpuscular volume
PT-INR = prothrombin time - international normalized ratio
PTT = partial thromboplastin time
RBC = red blood cell count
WBC = white blood cell count

Table 14-4: Parameters and time points for biomarker investigations in study Part 1 / dose escalation (all comer)

Parameters	Screening	Treatment							Follow-up EOT visit
TUMOR TISSUE:		**Cycle 2, Day 1**							
p-ERK1/2 levels, ~~Tumor DNA~~	X(A)	X(B)							
		Cycle 1				**Cycle ≥2**			
Blood (serum) samples *:		D1	D3	D8	D15	D1	D8	D15	
…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…

…

Table 14-5: Parameters and time points for biomarker investigations in study Part 1 / MTD expansion (all comer)

Parameters	Screening	Treatment							Follow-up EOT visit
TUMOR TISSUE:		**Cycle 2, Day 1**							
…	…	…							
…	…								
…	…								
		Cycle 1				**Cycle ≥2**			
Blood (serum) samples *:		D1	D3	D8	D15	D1	D8	D15	
…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…

…

Table 14-6: Parameters and time points for biomarker investigations in study Part 2 / MTD expansion (sqNSCLC + BC)

Parameters	Screening	Treatment			Follow-up EOT visit
TUMOR TISSUE:		**Cycle 2, Day 1**			
…	…	…			
…	…				
…	…				
		Each Cycle			
Blood (serum) samples*:		Day 1	Day 8	Day 15	
…	…	…	…	…	…
…	…	…	…	…	…

…

New text:

Table 14-4, Table 14-5, Table 14-6 and Table 14-7 provide the parameters and time points for the laboratory examinations (safety laboratory tests, biomarker investigations) to be performed during the study. Instructions for biomarker and PK sample collection, processing, storage and shipment will be described in a separate document (e.g. lab manual).

Table 14-4: Parameters and time points of laboratory examinations performed at local laboratory or study site (safety laboratory) – Study Part 1 and Part 2

Parameters	Screen-ing	Treatment				Follow-up	
		Cycle 1	Each Cycle			EOT	FU
		Day -3	Day 1	Day 8	Day 15	visit	visit
BLOOD							
Hematology: …	X	X	X	X	X	X	X
Coagulation: PT or PT-INR (obligatory at screening) and PTT (aPTT)[A]	X	X	X	X	X	X	X
Biochemistry: Biochemistry: AST / GOT, ALT / GPT, gamma-GT, AP, LDH, amylase, lipase, glucose, triglycerides, creatinine[B], BUN, uric acid, bilirubin (total & direct), total protein, albumin, sodium, potassium, chloride, CPK, calcium, phosphate	X	X	X	X	X	X	X
Virology: …	X						
URINE							
Macroanalysis:	X	X	X	X	X	X	X
Urinalysis (dip stick): pH, blood, protein, glucose, bilirubin, urobilinogen, ketone, nitrite, leucocytes (or leucocyte esterase), specific gravity	X	X	X	X	X	X	X
Laboratory analysis[C]: …	X	X	X	X	X	X	X
Microscopic urinalysis[D]: …	X	X	X	X	X	X	X
Pregnancy test[F]	X						

(A) **…**
(B) **…**
(C) **…**
(D) **…**
(F) **…**

ALT / GPT = alanine aminotransferase / glutamic pyruvic transaminase
anti-HCV = hepatitis C virus antibodies
anti-HIV 1+2 = human immune deficiency virus 1 and 2 antibodies
AP = alkaline phosphatase
AST / GOT = aspartate aminotransferase / glutamic oxaloacetic transaminase
BUN = blood urea nitrogen
CPK = creatine phosphokinase
CRP = C-reactive protein
gamma GT = gamma glutamyl transferase
HBsAg = hepatitis B virus surface antigen
MCH = mean corpuscular hemoglobin
MCHC = mean corpuscular hemoglobin concentration
MCV = mean corpuscular volume
PT-INR = prothrombin time - international normalized ratio
PTT / aPTT = partial thromboplastin time / activated partial thromboplastin time
RBC = red blood cell count
WBC = white blood cell count

Table 14-5: Parameters and time points for biomarker investigations in study Part 1 / dose escalation (all comer)

Parameters	Screening	Treatment							Follow-up EOT visit
TUMOR TISSUE:		**Cycle 2, Day 1**							
p-ERK1/2 levels	X(A)	X(B)							
		Cycle 1				**Cycle ≥2**			
Blood (serum) samples *:		D1	D3	D8	D15	D1	D8	D15	
…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…

…

Table 14-6: Parameters and time points for biomarker investigations in study Part 1 / MTD expansion (all comer)

Parameters	Screening	Treatment							Follow-up EOT visit
TUMOR TISSUE:		**Cycle 2, Day 1**							
…	…	…							
…	…								
…	…								
		Cycle 1				**Cycle ≥2**			
Blood (serum) samples *:		D1	D3	D8	D15	D1	D8	D15	
…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…

…

Table 14-7: Parameters and time points for biomarker investigations in study Part 2 / MTD expansion (sqNSCLC + BC)

Parameters	Screening	Treatment			Follow-up EOT visit
TUMOR TISSUE:		**Cycle 2, Day 1**			
…	…	…			
…	…				
…	…				
		Each Cycle			
Blood (serum) samples*:		Day 1	Day 8	Day 15	
…	…	…	…	…	…
…	…	…	…	…	…

…

15.2 Amendment 2

Date of amendment: 19 Mar 2014

15.2.1 Overview of changes

Modification 1: Type of packaging for test drug was modified

Rationale for introducing Modification 1

The available stability data of the IMPD shelf life study for 50mg tablets show superiority of Alu/Alu blister against HDPE bottles. Therefore, as a precaution until real time data are available in HDPE bottles for 200 mg tablets, clinical supplies of 200mg tablets are packaged in Alu/Alu-blister. Stability studies for 200mg tablets in both packaging materials have been started.

15.2.2 Changes to the protocol

List of all CSP sections affected by Modification 1:

Section 6.2

Old text:

Table 6-2: Identity of test drug (IMP): BAY 1163877 tablet formulation

Generic name / brand name / INN	…
Substance code number(s)	…
Material / formulation) number(s)	…
Galenical form / formulation / vehicle and reconstitution, if applicable	…
Composition	…
Strength (amount of drug per unit) or concentration	…
Type of packaging and content	HDPE bottles with screw cap closure
Marketing Authorization Holder if applicable	…

New text:

Table 6-2: Identity of test drug (IMP): BAY 1163877 tablet formulation

Generic name / brand name / INN	…
Substance code number(s)	…
Material / formulation) number(s)	…
Galenical form / formulation / vehicle and reconstitution, if applicable	…
Composition	…
Strength (amount of drug per unit) or concentration	…
Type of packaging and content	HDPE bottles with screw cap closure **or blisters of Foil 25/45/60 µm oPA/Al/PP (4320 / 0257) sealed to Foil 20 µm Al sealable to PP (4345 / 0202)**
Marketing Authorization Holder if applicable	…

15.3 Amendment 3

Date of amendment: 19 Jun 2014

15.3.1 Overview of changes

Modification 1: Expansion of indications for study Part 2

Rationale for introducing Modification 1

Preclinical data demonstrate a strong anti-tumor efficacy of BAY 1163877 not only in subjects with sqNSCLC and BC, but also in subjects with LAC or SCCHN. Protocol amendment 3 therefore expands the indications to evaluate biomarker status, PD parameters, and tumor response in Part 2 / MTD expansion from 2 specific populations (sqNSCLC + BC) to 4 specific populations (sqNSCLC + LAC + BC + SCCHN).

List of all CSP sections affected by Modification 1:

Due to the expansion from 2 to 4 indications in study Part 2, the term "sqNSCLC + BC" was replaced **throughout the text** by "sqNSCLC + LAC + BC + SCCHN".

Modification 2: Introduction of a second SIS / ICF for subjects recruited for the MTD expansion cohort of study Part 1 and Part 2

Rationale for introducing Modification 2

In this study, the information on subjects' FGFR expression level and the presence of activating mutations in FGFR encoding genes is a key prerequisite for subject stratification at screening. If subjects do not present the criteria required for stratification it is not necessary to perform all screening examinations and assessments. It was therefore decided to separate FGFR expression / FGFR mutation testing from screening procedures, and to introduce a separate SIS / ICF for FGFR expression / FGFR mutation testing which will only be used for subjects recruited for the MTD expansion cohort of Part 1 or Part 2. Due to this change, "FGFR expression / FGFR mutation testing" and "screening" have become two separate parts of the newly introduced generic term "pre-treatment" phase (see Section 7.1.2.1), and Section "Inclusion criteria" was divided in Section 5.1.1.1 "Eligibility criteria for FGFR expression / FGFR mutation testing" and Section 5.1.1.2 "Eligibility criteria for study treatment".

Additionally, it was clarified, that the evaluation of FGFR signaling pathway mutations (that may render a tumor drug-insensitive despite having high FGFR expression or an activating mutation) is planned retrospectively for subjects in the MTD expansion cohorts of both study parts, i.e. for subjects of Part 1 (all comer) and for subjects of Part 2 (sqNSCLC + LAC + BC + SCCHN).

List of all CSP sections affected by Modification 2:

- Synopsis
- Section 4

- Section 5.1.1
- Section 5.3
- Section 6.3
- Section 7.1.2
- Section 7.4.4
- Section 7.4.4.1
- Section 7.5.4.2
- Section 9.1
- Section 11.2
- Section 14.1
- Section 14.2

Modification 3: Modification of inclusion and exclusion criteria

Rationale for introducing Modification 3

Before, only subjects with amylase ≤ 1.5 x ULN and mild hepatic impairment (Child-Pugh score A) were eligible for the treatment period. The restriction was considered too strict for the target population (refractory, locally advanced or metastatic solid tumors). To improve subject recruitment, the criteria were changed to amylase ≤ 2.5 x ULN and not more than Child-Pugh score B7 to allow inclusion of subjects with more advanced pancreatic and hepatic impairment.

Monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) were added to the list of not allowed previous chemotherapy within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

List of all CSP sections affected by Modification 3:

- Synopsis
- Section 5.1.1
- Section 5.1.2
- Section 7.4.4
- Section 14.2

Modification 4: Additional evaluation of food effect on the pharmacokinetics of BAY 1163877

Rationale for introducing Modification 4

Food-effect bioavailability will be evaluated additionally to guide and select dosing regimen of BAY 1163877 in the further development. Evaluation of the effect of food on single-dose PK of BAY 1163877 is considered to impose only little extra burden on the study population. Approximately 8 subjects treated at MTD in Part 1 or Part 2 Part will be asked to participate in "Food effect assessment" with single-dose administration under fed and fasting conditions on Day -3 (after breakfast) respectively Day 1 (after an overnight fast) of Cycle 1.

List of all CSP sections affected by Modification 4:

- Synopsis
- Section 4
- Section 6.1
- Section 6.4.2.1
- Section 6.4.2.2
- Section 6.4.2.2.1 (new)
- Section 6.4.2.3
- Section 7.1.2.3
- Section 7.1.2.3.1
- Section 7.4.1.1
- Section 7.4.2.1
- Section 7.4.2.2
- Section 7.5.3.4
- Section 8.4.5
- Section 14.1

Modification 5: Additional evaluation of urinary excretion of BAY 1163877

Rationale for introducing Modification 5

To evaluate the amount of drug evaluated via urine, 24-hour urine collection will be done in approximately 8 subjects enrolled in Part 1 or Part 2 MTD expansion cohorts on Cycle 1, Day 1.

List of all CSP sections affected by Modification 5:

- Synopsis
- Section 4
- Section 7.1.2.3.1

- Section 7.4.2.1
- Section 7.4.2.2
- Section 8.4.5
- Section 14.1

Modification 6: Additional PK assessments for population PK / PD modeling

Rationale for introducing Modification 6

To obtain longitudinal exposure data for PK / PD modeling (together with occurrences of selected adverse events and documented clinical responses), two blood samples (one pre-dose and one post-dose) will be collected over 4 cycles (Cycles 2-5, Day 1) in all subjects participating in the MTD expansion cohorts of study Part 1 and Part 2

List of all CSP sections affected by Modification 6:

- Synopsis
- Section 4
- Section 7.1.2
- Section 7.4.2.1
- Section 7.4.2.2
- Section 8.6
- Section 14.1

Modification 7: Replacement of subjects

Rationale for introducing Modification 7

To ensure a sufficient number of subjects with paired biopsy samples for p-ERK1/2 analysis, subjects with insufficient paired biopsy samples in Study Part 1 / MTD expansion (all comer) will be replaced.

List of all CSP sections affected by Modification 7:

Section 5.2.2

Modification 8: Change in visit schedule starting with Cycle 13

Rationale for introducing Modification 8

Starting with Cycle 13, the number of site visits per cycle will be reduced from 3 visits (Days 1, 8 and 15) to 2 visits (Days 1 and 11). The reduction in visits may provide greater convenience for patients and is sufficient to evaluate safety in subjects who are already stable on treatment for several months.

List of all CSP sections affected by Modification 8:

- Synopsis
- Section 4

- Section 7.1.2
- Section 7.4.4
- Section 14.1
- Section 14.2

Modification 9: Change in time window for EOT visit

Rationale for introducing Modification 9

The EOT visit can also be conducted on the same day or shortly after diagnosed tumor progression / other reasons for discontinuation. A time window of 7 days is not mandatory. Therefore, the time window for the EOT visit will be changed from 7-14 days to 0-14 days after last dose.

List of all CSP sections affected by Modification 9:

- Synopsis
- Section 4
- Section 7.1.2
- Section 14.1
- Section 14.2

Modification 10: Minor corrections

Rationale for introducing Modification 10

Minor text modifications and corrections of omissions regarding virology testing, measurement of body weight and electronic data transfer, or terminology were done for clarification and to ensure correct and consistent wording.

List of all CSP sections affected by Modification 10:

List of abbreviations

Section 6.4.2

Section 6.7

Section 6.9.1

Section 7.1.2

Section 7.5.1.3

Section 7.5.4.2

Section 7.6.1

Section 9.1

Section 12

Section 14.1

Section 14.2

15.3.2 Changes to the protocol

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol.

In the display of modifications, the “old text” refers to the protocol version preceding this amendment. Deletions are crossed out in the “old text”. Additions are underlined in the “new text”.

The replacement of the term “sqNSCLC + BC” by “sqNSCLC + LAC + BC + SCCHN” throughout the protocol (see Section 15.1.1, Modification 1) and corrections of typing errors, omissions or terminology (minor corrections) are not highlighted in this amendment.

Synopsis

This section was changed as a result of Modifications 1-6, 8 and 9.

Old text:

Title	**…**
Short title	**…**
Clinical study phase	**…**
Project number	**…**
Study objective(s)	**…**
Test drug(s)	**…**
Name of active ingredient	**…**
Formulation IMP 1	**…**
Formulation IMP 2	**…**
Dose(s)	**…**
Route of administration	**…**
Duration of treatment	**…** Duration and dosing schedule of subjects enrolled for tablet relative bioavailability assessment (“tablet bridging cohort”) of study Part 1: **…** Duration and dosing schedule for subjects of study Part 2 without PK assessment: **…**
Reference drug (s)	**…**
Indication	**…**

Diagnosis and main criteria for inclusion	Inclusion criteria: • Signed ~~informed consent (~~IC~~)~~ obtained before any study specific procedure. ~~Subjects must be able to understand and willing to sign the written IC.~~ • Subjects with histologically or cytological confirmed, refractory, locally advanced or metastatic solid tumors who are not candidates for standard therapy. – ~~*Study Part 1 / dose escalation + MTD expansion cohort (all comer):* Subjects with any type of solid tumor (all comer) will be eligible for dose escalation and dose expansion at MTD in Part 1; **Subjects enrolled for dose expansion (MTD expansion cohort "all comer") will be stratified** according to high fibroblast growth factor receptor (FGFR) expression levels and the presence or absence of additional genetic alterations in the FGFR signaling pathway using archival or fresh tumor biopsy material.~~ – ~~*Study Part 2 / MTD expansion cohort (sqNSCLC + BC)*: Subjects will be eligible for Part 2 only if they have histological or cytological confirmed squamous non-small cell lung cancer (sqNSCLC) or bladder cancer (BC).~~ ~~All subjects in Part 2 (MTD expansion cohort "sqNSCLC + BC") will be stratified according to high FGFR expression levels and the presence or absence of additional genetic alterations in the FGFR signaling pathway using archival or fresh tumor biopsy specimen.~~ ~~BC subjects with low overall FGFR expression levels can be included if activating FGFR3 mutations are confirmed.~~ • Subjects must have at least one measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. A lesion in a previously irradiated area is eligible and to be considered as measurable disease as long as there is objective evidence of progression of the lesion prior to study enrollment. • Subjects with resected primary tumors who have documented metastases are eligible. ~~Existence of an~~

Diagnosis and main criteria for inclusion **(continued)**	~~archival biopsy is mandatory for stratification of subjects included in the expansion cohorts at MTD in Part 1 (all comer) and Part 2 (sqNSCLC + BC). If no archival biopsy is available for a subject assigned to the MTD expansion cohort "all comer" (Part 1) respectively to the MTD expansion cohort "sqNSCLC + BC" (Part 2), fresh tumor biopsy material is required for stratification~~ • ~~A pre-treatment biopsy at screening and a second biopsy on Cycle 2, Day 1 will be obtained from all subjects who agreed on repeated biopsies.~~ ~~The following rules apply to subjects participating in study Part 1 and study Part 2:~~ • ~~*Study Part 1 / dose escalation (all comer)*:~~ ~~Biopsies for biomarker studies are optional for subjects enrolled to the dose-escalation cohorts.~~ • ~~*Study Part 1 / MTD expansion cohort (all comer)*:~~ ~~Both a pre-treatment biopsy (screening) and a second biopsy (Cycle 2, Day 1) for biomarker studies are mandatory for all subjects in the MTD expansion cohort. Material from the mandatory pre-treatment biopsy may be used for stratification of subjects if no archival biopsy is available at screening.~~ • ~~*Study Part 2 / MTD expansion cohort (sqNSCLC + BC)*:~~ ~~A pre-treatment biopsy for stratification is only mandatory for subjects for whom no archival biopsy is available.~~ • ~~Biopsies for biomarker studies are optional for all subjects with archival biopsies.~~ Note: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C ~~or~~ nitrosoureas should not be given within 6 weeks of pre-treatment biopsy. • Male or female subjects ≥ 18 years of age • …

Diagnosis and main criteria for inclusion **(continued)**	• … • ... • ... • Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting the study treatment: … … Amylase and lipase ≤ ~~1.5~~ x ULN Not more than ~~mild hepatic impairment,~~ Child-Pugh score ~~A~~ …
Study design	…
Methodology	Eligible cancer subjects will be enrolled at multiple centers in Europe and Asia. In total, the "on study" period for the subjects comprises 3 phases: • Screening ~~(minimum 7 days, maximum 28 days)~~ • Treatment *Study Part 1 / dose escalation + MTD expansion (all comer):* … *Study Part 1 /"tablet bridging cohort" (all comer)* … *Study Part 2 / MTD expansion (sqNSCLC + BC):* … Note: Treatment with BAY 1163877 at MTD in Part 1 (expansion cohort "all comer") and Part 2 (expansion cohort "sqNSCLC + BC") can run in parallel. • Follow-up (FU) End of Treatment (EOT) visit ~~7~~ 14 days after last dose of BAY 1163877 …

Methodology **(continued)**	**Determination of the MTD:** **…** **Pharmacokinetics (PK):** Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 (up to 48 hours after dosing) in the "tablet bridging cohort", and on Cycle 1, Day 1 (up to 48 hours after dosing) and on Cycle 1, Day 15 (up to 12 hours after dosing), respectively, in all subjects participating in Study Part 1 (all comer) and in at least 12 subjects participating in Study Part 2 (sqNSCLC + BC). Plasma concentration of BAY 1163877 will be measured using a validated method. Exploratory monitoring of metabolites may also be performed in pooled plasma (most likely at the MTD or the therapeutic dose). ~~Specifically, if performed at the MTD, this will be done initially in 2 subjects (highest and lowest BAY 1163877 area under the curve (AUC)).~~ **Safety / tolerability:** **…** **Cardiovascular assessment:** **…** **Electrocardiogram (ECG):** 12-lead ECG readings will be performed at screening, on Cycle 1, Days -3 and -2 ("tablet bridging cohort" only), on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle, and at the EOT visit. **At screening...** **Pharmacodynamic (PD) biomarkers:** **…** **Biomarker analysis in serum** Blood Blood (serum) samples for quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected at screening, on Days 1*, 8* and 15* of ~~each Cycle~~, and at EOT visit. In **…** * Blood collection before administration of morning dose

Methodology **(continued)**	**<u>Biomarker analysis in serum</u>** Blood Blood (serum) samples for quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected at screening, on Days 1*, 8* and 15* of ~~each Cycle~~, and at EOT visit. In **…** * Blood collection before administration of morning dose **<u>Biomarker analysis in tumor tissue</u>** Biomarker analysis will be done at screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + BC) according to FGFR expression levels / ~~pathway~~ mutation~~s~~ using either an archival or fresh tumor biopsy material (see inclusion criteria). Analysis of **…** **<u>Tumor response evaluation:</u>** **...** **<u>Recommended Phase II dose (RP2D):</u>** **...**
Type of control	**…**
Number of subjects	... • Study Part 1 / dose escalation (all comer): …. • Study Part 1 / MTD expansion (all comer): ... • *Study Part 2 / MTD expansion (sqNSCLC + BC)*: 40 additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC and 20 evaluable subjects with BC treated at MTD.
Primary variables	<u>Determination of MTD</u> **…**

Primary variables **(continued)**	Pharmacokinetics: (BAY 1163877) **On Cycle 1 Day -3 ("tablet bridging cohort" only) and Cycle 1, Day 1:** C_{max}, AUC(0-12), AUC(0-t_{last}), AUC and corresponding dose adjusted parameters (C_{max}/D, AUC(0-12)/D AUC(0-t_{last})/D, AUC/D and AUC). For Cycle 1, Day 15: $C_{max,md}$, C_{max}/D_{md}, AUC(0-12)$_{md}$, AUC(0-12)/D_{md}, AUC(0-t_{last})$_{md}$, and AUC(0-t_{last})/D_{md}
Plan for statistical analysis	**…** To investigate dose proportionality an ANOVA will be performed on the log-transformed values of appropriate PK parameters and 90% confidence intervals will be derived.

New text:

Title	**…**
Short title	**…**
Clinical study phase	**…**
Project number	**…**
Study objective(s)	**…**
Test drug(s)	**…**
Name of active ingredient	**…**
Formulation IMP 1	**…**
Formulation IMP 2	**…**
Dose(s)	**…**
Route of administration	**…**

Duration of treatment	**…** Duration and dosing schedule of subjects enrolled for tablet relative bioavailability assessment ("tablet bridging cohort") of study Part 1: **…** Duration and dosing schedule of subjects enrolled for food effect assessment in the MTD expansion cohorts of study Part 1 and Part 2: 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. Duration and dosing schedule for subjects of study Part 2 without PK assessment: **…**
Reference drug (s)	**…**
Indication	**…**
Diagnosis and main criteria for inclusion	Inclusion criteria: Eligibility criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 1 and Part 2) • Ability to understand and willingness to sign the written subjects information sheet / informed consent form (SIS / ICF) for FGFR expression / FGFR mutation testing. Signed informed consent (IC) has to be obtained before any study specific procedure. • Subjects with histologically or cytological confirmed, refractory, locally advanced or metastatic solid tumors (all comer for study Part1; sqNSCLC, LAC, BC or SCCHN for Part 2) who are not candidates for standard therapy. • Male or female subjects ≥18 years of age

Diagnosis and main criteria for inclusion **(continued)**	• Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2 • Life expectancy of at least 3 months • Existence of archival or fresh tumor biopsy specimen for FGFR expression / FGFR mutation testing Besides these basic criteria, any criterion as outlined below already known to prohibit the patient's participation in the study should be considered. Eligibility criteria for study treatment • Ability to understand and willingness to sign the written SIS / ICF for study treatment eligibility. Signed IC obtained before any study specific procedure. • Subjects with histologically or cytological confirmed, refractory, locally advanced or metastatic solid tumors who are not candidates for standard therapy. Subjects with any type of solid tumors (all comer) will be eligible for dose escalation and dose expansion at MTD in Part 1. • Subjects enrolled in the MTD expansion cohorts of Study Part 1 and Part 2 must present high FGFR expression levels based on archival or fresh tumor biopsy specimen analysis. Bladder cancer subjects with low overall FGFR expression levels can be included if activating FGFR3 mutations are confirmed. **(only for MTD expansion cohorts of study Part 1 (all comer) and Part 2 (sqNSCLC + LAC +BC + SCCHN))** • Subjects must have at least one measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. A lesion in a previously irradiated area is eligible and to be considered as measurable disease as long as there is objective evidence of progression of the lesion prior to study enrollment. • Subjects with resected primary tumors who have documented metastases are eligible.

Diagnosis and main criteria for inclusion **(continued)**	• Subjects consent to undergo a paired biopsy at screening and on Cycle 2, Day 1 (only for MTD expansion cohorts of study Part 1 (all comer) Note: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies. • Male or female subjects ≥ 18 years of age • …
Diagnosis and main criteria for inclusion **(continued)**	• … • ... • ... • Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting the study treatment: **…** **…** Amylase and lipase ≤ 2.5 x ULN Not more than Child-Pugh score B7 hepatic impairment **…**
Study design	**…**

Methodology	Eligible cancer subjects will be enrolled at multiple centers in Europe and Asia. In total, the "on study" period for the subjects comprises 3 phases: Pre-treatment FGFR expression / FGFR mutation testing Screening Treatment *Study Part 1 / dose escalation + MTD expansion (all comer):* … *Study Part 1 /"tablet bridging cohort" (all comer)* … *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN):* … *MTD expansion cohorts (study Part 1 and Part 2) / "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. Note: Treatment with BAY 1163877 at MTD in Part 1 (expansion cohort "all comer") and Part 2 (expansion cohort "sqNSCLC + LAC + BC + SCCHN") can run in parallel. • Follow-up (FU) End of Treatment (EOT) visit 0-14 days after last dose of BAY 1163877 … **Determination of the MTD:** …

Methodology **(continued)**	**Pharmacokinetics (PK):** Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 (up to 48 hours after dosing) in the "tablet bridging cohort", and on Cycle 1, Day 1 (up to 48 hours after dosing) and on Cycle 1, Day 15 (up to 12 hours after dosing), respectively, in all subjects participating in Study Part 1 (all comer) and in at least 12 subjects participating in Study Part 2 (sqNSCLC + LAC + BC + SCCHN). In approximately 8 subjects enrolled in MTD expansion cohorts (study Part 1 and Part 2), single dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 (up to 48 hours after dosing) and on Cycle 1, Day 1 (up to 48 hours after dosing) for food effect assessment. Plasma concentration of BAY 1163877 will be measured using a validated method. In approximately 8 subjects enrolled in MTD expansion cohorts (study Part 1 and Part 2), urine will be collected for 24 hours after dosing on Cycle 1, Day 1 (concurrently with plasma PK samples) and analyzed using validated method. Exploratory monitoring of metabolites may also be performed in pooled plasma (most likely at the MTD or the therapeutic dose) and urine samples. **Safety / tolerability:** **…** **Cardiovascular assessment:** **…** **Electrocardiogram (ECG):** 12-lead ECG readings will be performed at screening, on Cycle 1, Days -3 and -2 ("tablet bridging cohort" and "food effect assessment" only), on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle, and at the EOT visit. **At screening...** **Pharmacodynamic (PD) biomarkers:** **...**

Methodology **(continued)**	**Biomarker analysis in serum** Blood serum) samples for quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected at screening, on Days 1*, 8* and 15* of Cycles 1-12, on Days 1 and 11 of Cycles ≥13, and at EOT visit. In **…** * Blood collection before administration of morning dose only for Cycle 1 of Part 1 and Part 2. **Biomarker analysis in tumor tissue** Biomarker analysis will be done at screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN) according to FGFR expression levels / FGFR mutation using either an archival or fresh tumor biopsy material (see inclusion criteria). Analysis of **…** **Tumor response evaluation:** **...** **Recommended Phase II dose (RP2D):** **...**
Type of control	**…**
Number of subjects	... • Study Part 1 / dose escalation (all comer): …. • Study Part 1 / MTD expansion (all comer): ... • *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)*: 40 additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and a cohort of 20 evaluable subjects with BC or SCCHN treated at MTD (at least 8 subjects per indication).

Primary variables	Determination of MTD **…** Pharmacokinetics: (BAY 1163877) **On Cycle 1 Day -3 ("tablet bridging cohort" and "food effect assessment" only) and Cycle 1, Day 1:** C_{max}, AUC(0-12), AUC(0-t_{last}), AUC and corresponding dose adjusted parameters (C_{max}/D, AUC(0-12)/D AUC(0-t_{last})/D, AUC/D and AUC) Amount of BAY 1163877 excreted renally during 0 to 12 h ($A_{E,ur}$(0-12)), 12 to 24 h ($A_{E,ur}$(12-24)) and 0 to 24 h ($A_{E,ur}$(0-24)) post-dose will be calculated at the MTD and also expressed as percent of dose administered. **For Cycle 1, Day 15:** $C_{max,md}$, C_{max}/D_{md}, AUC(0-12)$_{md}$, AUC(0-12)/D_{md}, AUC(0-t_{last})$_{md}$, and AUC(0-t_{last})/D_{md}.
Plan for statistical analysis	**…** To investigate dose proportionality, bioavailability and food effect an ANOVA will be performed on the log-transformed values of appropriate PK parameters and 90% confidence intervals will be derived.

Section 1: Introduction

This section was changed as a result of Modification 1.

Old text:

Background information

…

FGFRs are commonly altered in various human tumor diseases, including FGFR1 amplification in ~~squamous~~ non-small cell lung cancer (sqNSCLC (3)(4)), or activating mutations of FGFR3 in bladder cancers (5)(6)(7).

…

Rationale of the study

The target indications for BAY 1163877 in the expansion phase of this study are sqNSCLC ~~and bladder cancer (~~BC~~)~~. Preclinical data demonstrate a strong anti-tumor efficacy of BAY 1163877 in both tumor types as a single agent. In human sqNSCLC, amplification of FGFR1 has been demonstrated in up to 21% of cases (8)(9)(10)(11), which is usually detected by FISH-based analysis of gene copy number alterations.

…

New text:

Background information

…

FGFRs are commonly altered in various human tumor diseases, including FGFR1 amplification in non-small cell lung cancer (e.g. sqNSCLC (3)(4)), squamous cell carcinoma of the head and neck (SCCHN (38)), or activating mutations of FGFR3 in bladder cancers (BC(5)(6)(7)).

…

Rationale of the study

The target indications for BAY 1163877 in the expansion phase of this study are sqNSCLC, lung adenocarcinoma (LAC), BC and SCCHN. Preclinical data demonstrate a strong anti-tumor efficacy of BAY 1163877 in both tumor types as a single agent. In human sqNSCLC, amplification of FGFR1 has been demonstrated in up to 21% of cases(8)(9)(10)(11), and FGFR1 amplification was found in 15 % of SCCHN cases (38) which is usually detected by FISH-based analysis of gene copy number alterations.

…

Section 4: Study design - amended

This section was changed as a result of Modification 1, 2, 4, 5, 6, 8 and 9.

Old text:

Design overview

…

Targeted / planned enrollment:

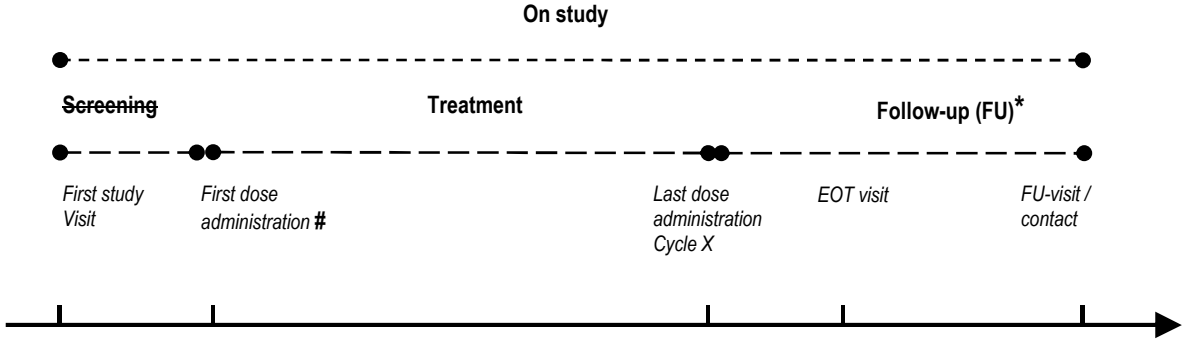
- Study Part 1 / dose escalation (all comer): **...**
- Study Part 1 / MTD expansion (all comer): **...**
- *Study Part 2 / MTD expansion (sqNSCLC + BC)*: 40 additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC and 20 evaluable subjects with BC treated at MTD.

PK assessments will be performed in all subjects participating in study Part 1 / dose escalation and MTD expansion (all comer). Additionally, PK assessments are planned in at least 12 subjects participating in study Part 2 / MTD expansion (sqNSCLC + BC) such that valid PK data are available in 8 subjects.

…

Study periods:

Figure 4-1: Schematic presentation of the treatment design



The first dose will be administered on Cycle 1, Day 1, except for subjects participating in relative bioavailability assessment who will receive ~~a single dose administered as tablet formulation~~ on Cycle 1, Day -3.

*Follow-up:
- EOT (End of Treatment) visit within ~~7~~ 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 4-1):

- Screening (minimum 7 days, maximum 28 days)

- Treatment

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

...

  Study Part 1 / "tablet bridging cohort" (all comer):

...

  Study Part 2 / MTD expansion (sqNSCLC + BC):

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

- Follow-up (FU)

  End of Treatment (EOT) visit ~~7~~-14 days after last dose of BAY 1163877

  …

The first screening visit is scheduled within 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 and ends with the last day when the study medication is administered in Cycle X. The length of treatment period **…**

…

An End of Treatment (EOT) visit will be performed for all subjects within ~~7~~-14 days after administration of the last dose of BAY 1163877. **…**

Treatment: **…**

…

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.

Subjects without PK assessment **...**

...

Determination of the maximum tolerated dose (MTD)

...

Pharmacokinetics (PK): Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 in the "tablet bridging cohort", and on Cycle 1, Days 1 and 15 in all subjects participating in Part 1 (all comer) and in at least 12 subjects participating in Part 2 (sqNSCLC + BC).

Plasma concentration of BAY 1163877 will be measured using a validated method.

Exploratory monitoring of metabolites may also be performed in pooled plasma samples (most likely at the MTD or the therapeutic dose). ~~Specifically, if performed at the MTD, this will be done initially in 2 subjects (highest and lowest BAY 1163877 area under the curve (AUC))~~.

The time points for PK sampling and further details are provided in Section 7.4.2.1.

Safety / tolerability:

...

Cardiovascular assessment:

...

Electrocardiogram (ECG): 12-lead ECG readings will be performed at screening, on Cycle 1, Days -3 and -2 ("tablet bridging cohort" and "food effect assessment", only), on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle, and at the EOT visit. **…**

…

Pharmacodynamic (PD) biomarkers: …

…

Biomarker analysis in serum: Blood (serum) samples for quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected at screening, on Days 1, 8 and 15 of ~~each Cycle~~, and at EOT visit. **…**

Biomarker analysis in tumor tissue: Biomarker analysis will be done screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + BC) according to FGFR expression levels / ~~pathway~~ mutation~~s~~ using either an archival tumor tissue specimen or fresh tumor biopsy material (see Section 5.1.1, inclusion criteria).

Analysis of phospho-extracellular signal-regulated kinase 1/2 levels, (p-ERK1/2) will be done at screening and on Cycle 2, Day 1 for all subjects who are willing to undergo a biopsy both at screening and on Cycle 2, Day 1. Both biopsies are mandatory for "all comer" subjects included in the MTD expansion cohort of Part 1.

Tumor response evaluation: …

…

Recommended Phase II dose (RP2D):

…

New text:

Design overview

…

Targeted / planned enrollment:

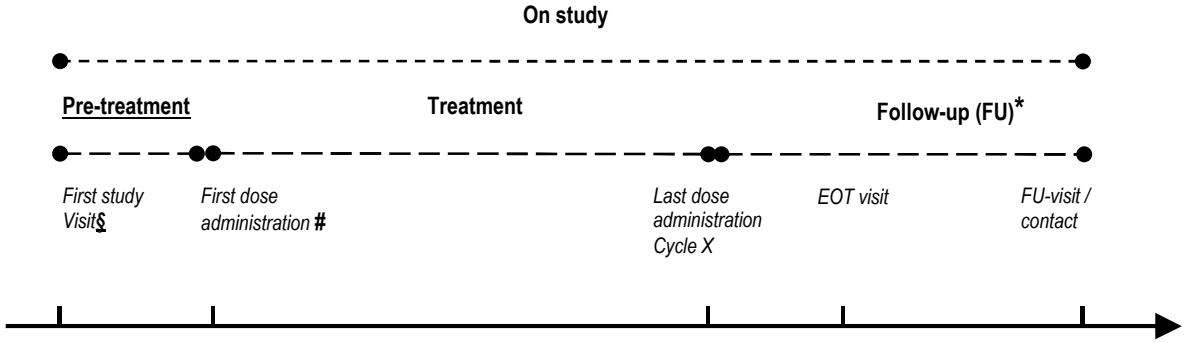
- Study Part 1 / dose escalation (all comer): **...**
- Study Part 1 / MTD expansion (all comer): **...**
- *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)*: 40 additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and 20 evaluable subjects with BC or SCCHN (at least 8 subjects per indication) treated at MTD.

PK assessments will be performed in all subjects participating in study Part 1 / dose escalation and MTD expansion (all comer). 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. 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 2 MTD expansion cohorts (Part 1 and Part 2) 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). The dose needs to be taken under supervision and the time recorded.

Study periods:

Figure 4-1: 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 4-1):

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

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

…

Study Part 1 / "tablet bridging cohort" (all comer):

…

Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN):

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.

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

- Follow-up (FU)

  … End of Treatment (EOT) visit 0-14 days after last dose of BAY 1163877

  …

The first screening visit is scheduled within 7 days / within 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 (please refer to Section 11.2). The screening period ends just before start of treatment.

The treatment period starts on the day of the first administration of study treatment either 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 **…**

…

An End of Treatment (EOT) visit will be performed for all subjects within 0-14 days after administration of the last dose of BAY 1163877. **…**

Treatment: **…**

…

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 **...**

...

Determination of the maximum tolerated dose (MTD)

...

Pharmacokinetics (PK): Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 in the "tablet bridging cohort",

and on Cycle 1, Days 1 and 15 in all subjects participating in Part 1 (all comer) and in at least 12 subjects participating in Part 2 (sqNSCLC + LAC + BC + SCCHN). In approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2), the effect of food on the PK of BAY 1163877 will be determined by comparing exposures on Cycle 1 Day -3 (administration after consumption of a high-fat, high-calorie breakfast) and Cycle 1 Day 1 (administration after an overnight fast of at least 8 hours), see Section 6.1.

Plasma concentration of BAY 1163877 will be measured using a validated method.

In approximately 8 subjects enrolled in MTD expansion cohorts (study Part 1 and Part 2), urine will be collected for 24 hours after dosing on Cycle 1, Day 1 (concurrently with plasma PK samples) and analyzed using validated method.

Exploratory monitoring of metabolites may also be performed in pooled plasma samples (most likely at the MTD or the therapeutic dose) and urine samples.

The time points for PK sampling and further details are provided in Section 7.4.2.1.

Safety / tolerability:

...

Cardiovascular assessment:

...

Electrocardiogram (ECG): 12-lead ECG readings will be performed at screening, on Cycle 1, Days -3 and -2 ("tablet bridging cohort" and "food effect assessment", only), on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle, and at the EOT visit. **…**

…

Pharmacodynamic (PD) biomarkers: …

…

Biomarker analysis in serum: Blood (serum) samples for quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected at screening, on Days 1, 8 and 15 of Cycles 1-12, on Days 1 and 11 of Cycles ≥13, and at EOT visit.

Biomarker analysis in tumor tissue: Biomarker analysis will be done screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN) according to FGFR expression levels / FGFR mutation using either an archival tumor tissue specimen or fresh tumor biopsy material (see Section 5.1.1, inclusion criteria).

Analysis of phospho-extracellular signal-regulated kinase 1/2 levels, (p-ERK1/2) will be done at screening and on Cycle 2, Day 1 for all subjects who are willing to undergo a biopsy both at screening and on Cycle 2, Day 1. Both biopsies are mandatory for "all comer" subjects included in the MTD expansion cohort of Part 1 (please refer to Section 5.1.1 for details).

Tumor response evaluation: …

…

Recommended Phase II dose (RP2D):

…

Section 5.1.1: Inclusion criteria

This section was changed as a result of Modifications 1 and 2.

Old text:

Screening must be performed within 28 days prior to the first dose of study drug. Subjects must fulfill all of the following criteria before being included in the treatment phase (i.e, before receiving any dose of BAY 1163877):

- Signed informed consent (IC) obtained before any study specific procedure. Subjects must be able to understand and willing to sign the written IC.

- Subjects with histologically or cytological confirmed, refractory, locally advanced or metastatic solid tumors who are not candidates for standard therapy.

  - ~~*Study Part 1 / dose escalation + MTD expansion cohort (all comer):* Subjects with any type of solid tumors (all comer) will be eligible for dose escalation and dose expansion at MTD in Part 1; **Subjects enrolled for dose expansion (MTD expansion cohort "all comer") will be stratified** according to high fibroblast growth factor receptor (FGFR) expression levels and the presence or absence of additional genetic alterations in the FGFR signaling pathway using archival or fresh tumor biopsy material.~~

  - ~~*Study Part 2 / MTD expansion cohort (sqNSCLC + BC):* Subjects will be eligible for Part 2 only if they have histological or cytological confirmed squamous non-small cell lung cancer (sqNSCLC) or bladder cancer (BC).~~
    ~~**All subjects in Part 2 (MTD expansion cohort "sqNSCLC + BC") will be stratified** according to high FGFR expression levels and the presence or absence of additional genetic alterations in the FGFR signaling pathway using archival or fresh tumor biopsy specimen.~~
    ~~BC subjects with low overall FGFR expression levels can be included if activating FGFR3 mutations are confirmed.~~

- Subjects must have at least one measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. A lesion in a previously irradiated area is eligible and to be considered as measurable disease as long as there is objective evidence of progression of the lesion prior to study enrollment.

- Subjects with resected primary tumors who have documented metastases are eligible.

- Existence of an archival biopsy is mandatory for stratification of subjects included in the expansion cohorts at MTD in Part 1 (all comer) and Part 2 (sqNSCLC + BC). If no

archival biopsy is available for a subject assigned to the MTD expansion cohort "all comer" (Part 1) respectively to the MTD expansion cohort "sqNSCLC + BC" (Part 2), fresh tumor biopsy material is required for stratification.

- A pre-treatment biopsy at screening and a second biopsy on Cycle 2, Day 1 will be obtained from all subjects who agreed on repeated biopsies.

The following rules apply to subjects participating in study Part 1and study Part 2:

Study Part 1 / dose escalation (all comer):

- Biopsies for biomarker studies are optional for subjects enrolled to the dose-escalation cohorts.

Study Part 1 / MTD expansion cohort (all comer):

- ~~Both a pre-treatment biopsy (screening) and a second biopsy (Cycle 2, Day 1) for biomarker studies are mandatory for all subjects in the MTD expansion cohort. Material from the mandatory pre-treatment biopsy may be used for stratification of subjects if no archival biopsy is available at screening.~~

Study Part 2 / MTD expansion cohort (sqNSCLC + BC):

- ~~A pre-treatment biopsy for stratification is only mandatory for subjects for whom no archival biopsy is available.~~
- ~~Biopsies for biomarker studies are optional for all subjects with archival biopsies.~~

Note: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C ~~or~~ nitrosoureas should not be given within 6 weeks of pre-treatment biopsy.

…

- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting the study treatment:

  …

  - Amylase and lipase ≤ ~~1.5~~ x ULN
  - Not more than ~~mild hepatic impairment,~~ Child-Pugh score ~~A~~
  - **…**

New text:

5.1.1.1 Eligibility criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 1 and Part 2)

- Ability to understand and willingness to sign the written subject information sheet / informed consent form (SIS / ICF) for FGFR expression / FGFR mutation testing (see Section 11.2). Signed informed consent (IC) has to be obtained before any study specific procedure.

- Subjects with histologically or cytological confirmed, refractory, locally advanced or metastatic solid tumors (all comer for study Part1; sqNSCLC, LAC, BC or SCCHN for Part 2) who are not candidates for standard therapy.
- Male or female subjects ≥18 years of age
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2
- Life expectancy of at least 3 months
- Existence of archival or fresh tumor biopsy specimen for FGFR expression / FGFR mutation testing
-

Besides these basic criteria, any criterion as outlined below under inclusion and exclusion criteria (Sections 5.1.1.2 and 5.1.2) already known to prohibit the patient's participation in the study should be considered.

5.1.1.2 Eligibility criteria for study treatment

Screening for study treatment eligibility must be performed within 7 days / within 28 days prior to the first dose of study drug. Subjects must fulfill all of the following criteria before being included in the treatment phase (i.e, before receiving any dose of BAY 1163877):

- Ability to understand and willingness to sign the written SIS / ICF for study treatment eligibility. Signed IC obtained before any ~~further~~ study specific procedure.
- Subjects with histologically or cytological confirmed, refractory, locally advanced or metastatic solid tumors who are not candidates for standard therapy.
Subjects with any type of solid tumors (all comer) will be eligible for dose escalation and dose expansion at MTD in Part 1.
- Subjects enrolled in the MTD expansion cohorts of Study Part 1 and Part 2 must present high FGFR expression levels based on archival or fresh tumor biopsy specimen analysis.
Bladder cancer subjects with low overall FGFR expression levels can be included if activating FGFR3 mutations are confirmed.
(only for MTD expansion cohorts of study Part 1 (all comer) and Part 2 (sqNSCLC + LAC +BC + SCCHN))
- Subjects must have at least one measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. A lesion in a previously irradiated area is eligible and to be considered as measurable disease as long as there is objective evidence of progression of the lesion prior to study enrollment.
- Subjects with resected primary tumors who have documented metastases are eligible.
- Subjects consent to undergo a paired biopsy at screening and on Cycle 2, Day 1
(only for MTD expansion cohorts of study Part 1(all comer))

Note: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

…

- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting the study treatment:

…

Amylase and lipase ≤ 2.5 x ULN

Not more than Child-Pugh score B7 hepatic impairment

…

Section 5.1.2: Exclusion criteria

This section was changed as a result of Modification 1 and 3.

Old text:

Subjects are to be excluded from the study if they display any of the following criteria:

Medical and surgical history

- For "all comer" subjects to be enrolled in study Part 1 / MTD expansion:
  - ~~No consent to mandatory biopsies at screening and on Cycle 2, Day 1.~~
  - ~~Low FGFR expression levels quantified by RNA in situ hybridization (RNAscope score ≤ 3).~~
- For subjects with sqNSCLCto be enrolled in study Part 2 / MTD expansion:
  - ~~No archival biopsy available and no consent to pre-treatment biopsy.~~
  - ~~Low FGFR expression levels quantified by RNA in situ hybridization (RNAscope score ≤ 3).~~
- For subjects with BC to be enrolled in study Part 2 / MTD expansion:

~~No archival biopsy available and no consent to pre-treatment biopsy.~~

~~Low FGFR expression levels quantified by RNA in situ hybridization (RNAscope score ≤ 3) and having no activating mutation in FGFR3 gene.~~

- Previous or concurrent cancer …

…

- Moderate and severe hepatic impairment, Child-Pugh B or C

…

Medication, drug use and special behavioral patterns

…

- Anticancer chemotherapy or immunotherapy during the study or within 5-half-lives prior to start of study treatment. Mitomycin C ~~or~~ nitrosoureas should not be given within 6 weeks of ~~start of study~~ treatment. Acute toxic effects **…**

…

New text:

Subjects are to be excluded from the study if they display any of the following criteria:

5.1.2.1 Exclusion criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 1)

- No archival biopsy available and no consent to obtain tumor biopsy.

- Subject still on anticancer treatment or in the washout period of a previous anticancer treatment (defined as 5 half-lives of the anticancer agent [or 6 weeks for monoclonal antibodies]) at the time the fresh biopsy would be obtained if no archival biopsy is available.

5.1.2.2 Exclusion criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 2)

- No archival biopsy available and no consent to obtain tumor biopsy.

5.1.2.3 Exclusion criteria

- FGFR testing shows low FGFR expression levels
(only for MTD expansion cohorts of study Part 1 (all comer) and Part 2 (sqNSCLC + LAC + SCCHN))

- No consent for mandatory paired biopsies for biomarker
(only for MTD expansion cohorts of study Part 1 (all comer))

- FGFR expression / FGFR mutation testing shows low FGFR expression levels and absence of activating mutation in FGFR3 gene
(only for Part 2 (BC))

Medical and surgical history

- Previous or concurrent cancer …

…

Medication, drug use and special behavioral patterns

…

- Anticancer chemotherapy or immunotherapy during the study or within 5-half-lives prior to start of study treatment. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies. Acute toxic effects **…**

…

Section 5.2.2: Replacement

This section was changed as a result of Modification 7.

Old text:

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 (see Section 6.7) 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.

New text:

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 (see Section 6.7) 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.

Section 5.3: Subject identification

This section was changed as a result of Modification 2.

Old text:

Each subject who signs a consent form for the study ~~and undergoes any screening procedure(s)~~ will be assigned a unique 9-digit screening number (SNR) in ascending order of recruitment into the study at that center. The first 2 digits will refer to the country, the subsequent 3 digits to the site number, and the following 4 digits will be subject identifiers.

…

New text:

Each subject who signs a consent form for the study will be assigned a unique 9-digit screening number (SNR) in ascending order of recruitment into the study at that center. The first 2 digits will refer to the country, the subsequent 3 digits to the site number, and the following 4 digits will be subject identifiers.

…

Section 6.1: Treatments to be administered - amended

This section was changed as a result of Modifications 1 and 4.

Old text:

In study Part 1 / dose escalation + MTD expansion (all comer), **…**

…

In study Part 2 / MTD expansion (sqNSCLC + BC), **…**

…

New text:

In study Part 1 / dose escalation + MTD expansion (all comer), **…**

…

In study Part 1 / MTD expansion (all comer), subjects will receive the MTD of BAY 1163877 determined at the end of dose escalation.

For the "food effect assessment", subjects will receive one single dose of BAY 1163877 on Cycle 1, Day -3 after consumption of a high-fat, high-calorie breakfast, and a second single dose BAY 1163877 on Cycle 1, Day 1 after an overnight fast of at least 8 hours. Further details are provided in Section 6.4.2.2.1.

In study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN), **…**

…

Section 6.3: Treatment assignment

This section was changed as a result of Modification 2.

Old text:

After completion of the screening examinations, subjects who meet the entry criteria will be placed in the current cohort at the specified dose level. A random list is not necessary because this is a non-randomized open label clinical trial. All subjects will be assigned a unique screening number (SNR), whether or not they are treated after the first signed informed consent. For subject identification, see Section 5.3.

New text:

After completion of the screening examinations, subjects who meet the entry criteria will be placed in the current cohort at the specified dose level. A random list is not necessary because this is a non-randomized open label clinical trial. All subjects will be assigned a unique screening number (SNR), whether or not they are treated after the first signed informed consent. For subject identification, see Section 5.3.

Section 6.4.2: Selection and timing of dose for each subject - amended

This section was changed as a result of Modifications 1 and 10.

Old text:

…. Dose escalation for subsequent cohorts will only be considered after ~~full evaluation of at least the first Cycle of~~ all subjects from the previous cohort.

Extent and duration of drug exposure of the individual subject in study Part 2 / dose expansion (sqNSCLC + BC) are given in Section 4.

New text:

…. Dose escalation for subsequent cohorts will only be considered after all subjects from the previous cohort have completed the first cycle or early discontinued.

Extent and duration of drug exposure of the individual subject in study Part 2 / dose expansion (sqNSCLC + LAC + BC + SCCHN) are given in Section 4.

Section 6.4.2.1: Dosing schedule - amended

This section was changed as a result of Modification 1 and 4.

Old text:

Study Part 2 / dose expansion (sqNSCLC + BC):

- …
- …

Evidence of tumor progression, **…**

New text:

Study Part 2 / dose expansion (sqNSCLC + LAC + BC + SCCHN):

- …
- …

Study Part 1 (MTD expansion cohort) or Study Part 2 / "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). BAY 1163877 will not be administered on Cycle 1, Day -2 and Day -1, in the evening of Cycle 1, Day 1 and on Cycle 1, Day 2.

Evidence of tumor progression, **…**

Section 6.4.2.2: Mode of administration - amended

This section was changed as a result of Modification 4.

Old text:

BAY 1163877 will be administered per os (p.o.) at least 1 hour before or 2 hours after a meal or snack.

The ready-to-use solution **…**

New text:

BAY 1163877 will be administered per os (p.o.) at least 1 hour before or 2 hours after a meal or snack. Subjects participating in "food effect assessment" will receive a single dose after consumption of high-fat, high-calorie meal (Cycle 1, Day -3) and a single dose after an overnight fast of at least 8 hours (Cycle 1, Day 1) see Section 6.4.2.2.1.

The ready-to-use solution **…**

Section 6.4.2.2.1: Food effect assessment

This section was changed as a result of Modification 4.

Old text:

Not applicable (new section).

New text:

To assess the effect of food on the PK of BAY 1163877, a single dose of BAY 1163877 will be administered immediately (within 5 minutes) after consumption of a high-fat, high-calorie breakfast on Cycle 1, Day -3 followed by PK profiling in subjects participating in the MTD expansion cohorts of study Part 1 and Part 2.

Examples of high-fat, high-calorie breakfast:

50 grams of smoked cooked ham, 30 grams of chicken liver sausage, 50 grams of rye bread, 7 ounces (210 mL) whole milk, 40 grams of butter, 30 grams of butter cheese and 17 Crispbread Wasa Mjölk

2 eggs (fried), 2 strips of bacon, 2 slices of bread toast, 8 ounces (240 mL) whole milk and 3 teaspoons of butter (for frying and for toast)

High-fat, high-calorie breakfast may be adapted depending on the country while maintaining similar fat and calorie content (approximately 50 % fat and 800 to 1000 calories). Breakfast should be consumed within 25 minutes. No snack is permitted for 4 hours after study drug administration.
BAY 1163877 will not be administered on Cycle 1, Day -2 and Day -1.
A single dose of BAY 1163877 will be administered on Cycle 1, Day 1 after an overnight fast of at least 8 hours (water is allowed *ad libitum*) followed by PK profiling. No food or snack is permitted for 4 hours after drug administration, but water is allowed 1 hour after dosing.

Study drug will not be administered in the evening of Cycle 1, Day 1 and on Cycle 1, Day 2 ("drug-free day").
Starting with Cycle 1, Day 3, BAY 1163877 will be taken twice daily (at least 1 hour before or 2 hours after a meal).

Section 6.4.2.3: Treatment duration - amended

This section was changed as a result of Modification 4.

Old text:

…

For subjects in the "tablet bridging cohort" treatment starts on Cycle 1, Day -3.

…

New text:

…

For subjects in the "tablet bridging cohort" and "food effect assessment", treatment starts on Cycle 1, Day -3.

…

Section 7.1.2: Timing of assessment

This section was changed as a result of Modifications 1, 2, 4, 5, 6, 8, 9 and 10.

Old text:

If not stated otherwise…

7.1.2.1 Screening

Pre-study examinations will be performed within 28 days before first administration of BAY 1163877 (i.e. before Cycle 1, Day 1) **...**

…

Study specific required screening examinations will only be performed after having received the subject's written ~~informed consent~~.

The following examinations will be performed prior to the first study drug administration:

Within 28 Days Prior to First Dose of BAY 1163877

- Signed informed consent (within 28 days or earlier)
- Inclusion / exclusion criteria
- Demographic data
- Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report
- Complete medical / oncological history, TNM classification (see Section 7.2.3)
- …
- ECOG performance status assessment
- …
- CT scans of the chest, abdomen and pelvis; CT scans of other metastatic lesions as applicable or MRI and documentation of lesion(s) according to RECIST, v1.1. CT/MRI scans prior screening can be used for documentation according to RECIST, v1.1, if scans were done the latest 28 days prior to first dose of BAY 1163877 (see Section 7.3.1)
- Obtain pre-treatment biopsy: mandatory for all subjects in the MTD expansion cohort of Part 1 (all comer), mandatory for all subjects in the MTD expansion cohort of Part 2 (sqNSCLC +BC) for whom no archival biopsy is available, voluntary for all other study subjects) depending on necessity of wash-out period of potential previous anti-cancer therapy and send to laboratory for biomarker evaluation, see Table 14–5, Table 14–6 and Table 14–7.
- Stratification of subjects to be enrolled in MTD expansion cohorts of Part 1 (all comer) and Part 2 (sqNSCLC +BC): Obtain archival tissue samples for subject stratification according to biomarker assessment. If no archival biopsy is available, material from a pre-treatment biopsy is required for stratification, see Table 14–6 and Table 14–7.

Within 7 Days Prior to First Dose of BAY 1163877

- …

7.1.2.2 Randomization

…

7.1.2.3 Treatment – amended

…

7.1.2.3.1 Cycle 1 - amended

For "tablet bridging cohort" cohort only:

Day -3 to Day -1 (possible overnight stay)

Day -3

- …
- Single oral administration of BAY 1163877 tablet formulation
- …

Days 1-3 (possible overnight stay)

Day 1

- …
- Measurement of body temperature and body weight (measurement of weight not required for subjects in the "tablet bridging cohort")
- …
- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2)
- Dispense of study medication (BAY 1163877) and diary

→ Oral administration of BAY 1163877 (single dosing for subjects with PK assessment, twice daily dosing for subjects without PK assessment)

- Toxicities / AE assessment and recording (if applicable)

Day 2

- **No administration of BAY 1163877 ("drug-free day") for subjects with PK assessment** (all subjects of study Part 1 and at least 12 subjects with PK assessment in study Part 2)
- …

7.1.2.3.2 Subsequent Cycles

Day 1 (Visit)

- ...
- Blood (serum) samples collection for biomarker tests, see Table 14–5 - Table 14–7
- Obtain second biopsy: mandatory for all subjects in the MTD expansion cohort of Part 1 (all comer), voluntary for all other subjects, and send to laboratory, see Table 14–5, Table 14–6 and Table 14–7.
- …

End of Every ~~Second~~ Cycle

- …

End of Cycle 2, then after every 3rd cycle

- …

7.1.2.3.3 Follow up

An End of Treatment (EOT) visit will be performed within ~~7~~-14 days after the last study drug administration.

…

Within ~~7~~-14 Days of Last Study Drug Administration (EOT Visit)

- …

New text:

7.1.2 Timing of assessment

If not stated otherwise **…**

…

7.1.2.1 Pre-treatment - amended

7.1.2.1.1 FGFR expression / FGFR mutation testing (MTD expansion cohorts only)

A separate subject information sheet / informed consent form (SIS / ICF) for FGFR expression / FGFR mutation testing must be signed by all subjects recruited for study Part 1 or Part 2 MTD expansion cohort (see Section 11.2).

The following activities / examinations will be performed prior to FGFR expression / FGFR mutation testing:

- Signed informed consent for FGFR expression / FGFR mutation testing
- Inclusion criteria limited to FGFR expression / FGFR mutation testing (see Section 5.1.1.1)
- ECOG performance status assessment
- Demographic data
- Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report
- Complete medical /oncological history, TNM classification (see Section 7.2.3)
- Obtain archival tumor tissue sample for FGFR expression / FGFR mutation testing

  Only, if no archival tumor tissue sample is available which has been handled and processed as described in the lab manual: Perform a biopsy to obtain fresh tumor material

- Toxicity / AE assessment and recording

All subjects enrolled into the study will be listed on a subject enrollment log provided by the sponsor's representatives.

7.1.2.1.2 Screening

Pre-study examinations will be performed within 7 days / within 28 days before first administration of BAY 1163877 (i.e. before Cycle 1, Day 1) **...**

…

Study specific required screening examinations will only be performed after having received the subject's written IC for study treatment eligibility. The subject information sheet / informed consent form (SIS / ICF) for study treatment eligibility must be signed by all subjects including those subjects presenting FGFR expression / FGFR mutation who have signed the SIS / ICF for FGFR expression / FGFR mutation testing before (see Section 7.1.2.1.1).

The following examinations will be performed prior to the first study drug administration:

Within 28 Days Prior to First Dose of BAY 1163877

- Signed informed consent for study treatment eligibility (within 28 days or earlier), see Section 11.2.
- Inclusion / exclusion criteria
- Demographic data (already collected for subjects of Part 1 or Part 2 MTD expansion cohorts, see Section 7.1.2.1.1)
- Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report (already done for subjects of Part 1 or Part 2 MTD expansion cohorts, see Section 7.1.2.1.1)
- Complete medical / oncological history, TNM classification (see Section 7.2.3) (already done for subjects of Part 1 or Part 2 MTD expansion cohorts, see Section 7.1.2.1.1)
- …
- ECOG performance status assessment (also for subjects of Part 1 or Part 2 MTD expansion cohorts, see Section 7.1.2.1.1)
- …
- CT scans of the chest, abdomen and pelvis; CT scans of other metastatic lesions as applicable or MRI and documentation of lesion(s) according to RECIST, v1.1. CT/MRI scans prior screening can be used for documentation according to RECIST, v1.1, if scans were done the latest 28 days prior to first dose of BAY 1163877 (see Section 7.3.1)
- Virology tests, for details see Table 14–4
- Obtain pre-treatment biopsy:

- optional for subjects in the dose escalation cohorts of study Part 1 (all comer)
- mandatory for all subjects in the MTD expansion cohort of Part 1 (all comer).
- optional for subjects in the MTD expansion cohort of Part 2 (sqNSCLC + LAC + BC + SCCHN)
- Note 1: A biopsy is mandatory for all subjects in the MTD expansion cohort of Part 1 and Part 2 for whom no archival biopsy is available for FGFR expression / FGFR mutation testing. Additional biopsy is not requested if a biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit (see Section 7.1.2.1.1).

  Note 2: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

Within 7 Days Prior to First Dose of BAY 1163877

- …

7.1.2.2 Randomization

…

7.1.2.3 Treatment – amended

…

7.1.2.3.1 Cycle 1 - amended

For "tablet bridging cohort" or "food effect assessment" only:

Day -3 to Day -1 (possible overnight stay)

Day -3

- …
- Single oral administration of BAY 1163877 tablet formulation ("tablet bridging cohort" only)
- Single oral administration of BAY 1163877 immediately after consumption of high-fat, high-calorie meal as specified in Section 6.4.2.2.1 ("food effect assessment" only)
- …

Days 1-3 (possible overnight stay)

Day 1

- …

- Measurement of body temperature and body weight (measurement of weight not required for subjects in the "tablet bridging cohort" and for subjects with "food effect assessment")
- …
- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2)
- Urine collection for PK analysis (to be performed in approximately 8 subjects in Part 1 or Part 2 MTD expansion cohorts, see Section 7.4.2.1)
- Dispense of study medication (BAY 1163877) and diary

→ **Oral administration of BAY 1163877 (single dosing for subjects with PK assessment, twice daily dosing for subjects without PK assessment)**

→ **Oral administration of a single dose of BAY 1163877 after at least 8 hours of overnight fast as specified in Section 6.4.2.2.1 ("food effect assessment" only)**

- Toxicities / AE assessment and recording (if applicable)

Day 2

- **No administration of BAY 1163877 ("drug-free day") for subjects with PK assessment** (all subjects of study Part 1 and at least 12 subjects with PK assessment in study Part 2 [including "food effect assessment"])
- …

7.1.2.3.2 Subsequent Cycles (Cycles 2-12)

Day 1 (Visit)

- Measurement of body temperature and body weight
- ...
- Blood (serum) samples collection for biomarker tests, see Table 14–5 - Table 14–7
- Only on Day 1 of Cycles 2, 3, 4 and 5: Blood (plasma) sample collection for exposure-response modelling at pre-dose and between 0.5 and 1.5 hours post-dose in all subjects participating in the MTD expansion cohorts of study Part 1 and part 2, see Table 14–3. The dose needs to be taken under supervision and the time recorded.
- Only on Day 1 of Cycle 2: Obtain second biopsy: mandatory for all subjects in the MTD expansion cohort of Part 1 (all comer), voluntary for all other subjects, and send to laboratory, see Table 14–5, Table 14–6 and Table 14–7.
- …

End of Cycle 2 and every 2nd subsequent Cycle (i.e., end of Cycles 2, 4, 6, 8, 10, 12)

- …

End of Cycle 2 and every 3rd subsequent Cycle (i.e., end of Cycles 2, 5, 8, 11)

- …

7.1.2.3.3 Subsequent Cycles (Cycles ≥13)

Day 1 (Visit)

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature and body weight
- 12-lead ECG, single reading (see Section 7.5.3.4)
- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Table 14-4
- Calculation of eGFR (see Section 14.9)
- Blood (serum) samples collection for biomarker tests, see Table 14-5 - Table 14-7
- Oral administration of BAY 1163877
- Toxicities / AE assessment and recording (if applicable)

Day 11 (Visit)

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- ECOG performance status
- Blood and urine collection for safety laboratory tests (repetitions for controls may be necessary), for details see Table 14-4
- Calculation of eGFR (see Section 14.9)
- Blood (serum) samples collection for biomarker tests, see see Table 14-5 - Table 14-7
- Oral administration of BAY 1163877
- Toxicities / AE assessment and recording (if applicable)

End of Cycle 14 and every 2nd subsequent Cycle (i.e., end of Cycles 14, 16, 18, …)

- Send subject to consultant ophthalmologist for ophthalmological examination and review certificate

End of Cycle 14 and every 3rd subsequent Cycle (i.e., end of Cycles 14, 17, 21, …)

- CT scans of the chest, abdomen and pelvis; CT scans of other metastatic lesions as applicable or MRI and documentation of response according to RECIST, v1.1 (see Section 7.3.1)

7.1.2.3.4 Follow up

An End of Treatment (EOT) visit will be performed within 0-14 days after the last study drug administration.

…

Within 0-14 Days of Last Study Drug Administration (EOT Visit)

- …

Section 7.4.1.1: Cardiovascular assessment - amended

This section was changed as a result of Modification 4.

Old text:

…

BP and HR will be measured at the following time points:

- Screening (one measurement within 7 days before start of treatment)
- Cycle 1, Day -3 to Day -1 ("tablet bridging cohort" only)

New text:

…

BP and HR will be measured at the following time points:

- Screening (one measurement within 7 days before start of treatment)
- Cycle 1, Day -3 to Day -1 ("tablet bridging cohort" and "food effect assessment" only)

Section 7.4.2.1: Drug measurements - amended

This section was changed as a result of Modifications 1, 4, 5 and 6.

Old text:

Pharmacokinetics of BAY 1163877 will be evaluated on Cycle 1, Day -3 ("tablet bridging cohort", only), Cycle 1, Day 1 after single-dose administration, and on Cycle 1, Day 15 after multiple-dose administration of BAY 1163877 at the respective dose level achieved during dose escalation.

Pharmacokinetic assessments will be performed in all subjects enrolled in Part 1 (dose escalation and MTD expansion (all comer) cohorts). The plan is to perform pharmacokinetic assessments in at least 12 subjects in Part 2 MTD expansion cohort (sqNSCLC + BC) such that valid PK data are available in 8 subjects.

Blood (plasma) samples for PK assessment of BAY 1163877 will be collected at the following time points:

- Cycle 1, Day -3 ("tablet bridging cohort" only): single-dose PK
  - …
- Cycle 1, Day 1: single-dose PK

  …
- Cycle 1, Day 15: multiple-dose PK

  …

…

When blood pressure measurement and PK sample collection are scheduled at the same time point, subject's blood pressure will be measured before collection of the PK sample

Plasma concentrations of BAY 1163877 will be measured using a validated method. Instructions for sample collection, processing, storage and shipment will be described in a separate document (e.g. lab manual).

Exploratory monitoring of metabolites may also be performed in pooled plasma samples (most likely at the MTD or the therapeutic dose). ~~Specifically, if performed at the MTD, this will be done initially in 2 subjects (highest and lowest BAY 1163877 area under the curve (AUC)).~~

New text

Pharmacokinetics of BAY 1163877 will be evaluated on Cycle 1, Day -3 ("tablet bridging cohort" and "food effect assessment", only), on Cycle 1, Day 1 after single-dose administration, and on Cycle 1, Day 15 after multiple-dose administration of BAY 1163877 at the respective dose level achieved during dose escalation.

Pharmacokinetic assessments will be performed in all subjects enrolled in Part 1 (dose escalation and MTD expansion (all comer) cohorts). The plan is to perform

pharmacokinetic assessments in at least 12 subjects in Part 2 MTD expansion cohort (sqNSCLC + LAC + BC + SCCHN) such that valid PK data are available in 8 subjects. "Food effect assessment" will be performed in approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2).

Blood (plasma) samples for PK assessment of BAY 1163877 will be collected at the following time points:

- Cycle 1, Day -3 ("tablet bridging cohort" and "food effect assessment" only): single-dose PK

…

- Cycle 1, Day 1: single-dose PK

- …

- Cycle 1, Day 15: multiple-dose PK

…

- Cycles 2-5, Day 1: exposure-response modelling
  - pre-dose (before supervised dose administration), and 1 (± 0.5) hour post-dose

…

When blood pressure measurement and PK sample collection are scheduled at the same time point, subject's blood pressure will be measured before collection of the PK sample

24-hour urine collection: In approximately 8 subjects of the MTD expansion cohorts (study Part 1 and Part 2), on Cycle 1 Day 1, complete urine output will be collected over 24 hours post administration in 0 to 12 hour and 12 to 24 hour intervals concurrently with plasma PK samples. For each subject, within each collection interval, the collected urine will be combined and the total volume of the combined urine will be determined.
A representative aliquot of the pooled urine will be used to determine the concentration of BAY 1163877.

Plasma and urine concentrations of BAY 1163877 will be measured using a validated method. Instructions for sample collection, processing, storage and shipment will be described in a separate document (e.g. lab manual).

Exploratory monitoring of metabolites may also be performed in pooled plasma samples (most likely at the MTD or the therapeutic dose) and in urine.

Section 7.4.2.2: Pharmacokinetic evaluation - amended

This section was changed as a result of Modification 1, 4, 5 and 6.

Old text:

Primary PK parameters (plasma): **BAY 1163877**

- **Cycle 1, Day -3 ("tablet bridging cohort") and Cycle 1, Day 1 single dose:**

C_{max}, C_{max}/D, AUC(0-12), AUC(0-12)/D,
AUC(0-t_{last}), AUC(0-t_{last})/D, AUC, and AUC/D
AUC may not be calculated if it is not possible to estimate half-life

…

Pre-dose plasma concentrations (if additionally collected) will be used for monitoring purpose only.

Pharmacokinetic evaluation - Population analysis

Pharmacokinetic data might be analyzed using nonlinear mixed effects models. Details of the model development and evaluation will be described in a separate Evaluation Plan and the results reported in a separate Evaluation Report.

New text:

Primary PK parameters (plasma): **BAY 1163877**

- **Cycle 1, Day -3 ("tablet bridging cohort" and "food effect assessment" only) and Cycle 1, Day 1 single dose:** C_{max}, C_{max}/D, AUC(0-12), AUC(0-12)/D, AUC(0-t_{last}), AUC(0-t_{last})/D, AUC, and AUC/D
AUC may not be calculated if it is not possible to estimate half-life

…

Pre-dose plasma concentrations (if additionally collected) will be used for monitoring purpose only.

Amount of BAY 1163877 excreted renally during 0 to 12 h (AE,ur(0-12)), 12 to 24 h (AE,ur(12-24)) and 0 to 24 h (AE,ur(0-24)) post-dose will be calculated at the MTD and also expressed as percent of dose administered.

Pharmacokinetic evaluation - Population analysis

Pharmacokinetic data might be analyzed using nonlinear mixed effects models. Details of the model development and evaluation will be described in a separate Evaluation Plan and the results reported in a separate Evaluation Report.

These samples collected on Day 1 of Cycles 2 through 5 at pre-dose and between 0.5 and 1.5 hours post-dose will document a longitudinal exposure under steady state condition. No detailed dosing history is required before the pre-dose sample, but the dose that separates the pre- and post-dose sample needs to be taken under supervision and the time recorded. The longitudinal exposure data will be used in exposure-response modelling of adverse events and clinical responses.

Section 7.4.4: Biomarker investigations - amended

This section was changed as a result of Modifications 1, 2, 3, and 8.

Old text:

…

Biomarker analysis in blood (serum) samples

Blood (serum) samples for the quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected as follows:

- Study Part 1 / dose escalation + MTD expansion (all comer)
  - …
  - …
  - Cycle ~~≥2~~: Days 1*, 8*, 15*
  - EOT visit
- Study Part 2 / MTD expansion (sqNSCLC + BC)
  - …
  - …
  - …
  - *Blood collection before administration of morning dose.

Biomarker analysis in TUMOR TISSUE

Biomarker analysis will be done at screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + BC) according to FGFR expression levels / ~~pathway~~ mutation~~s~~ using either an archival tumor tissue specimen or fresh tumor biopsy material (see Section 5.1.1: Inclusion criteria, and Section 7.4.4.1: Predictive marker investigation). **…**

- Study Part 1 / dose escalation (all comer):
  - …
  - …
- Study Part 1 / MTD expansion (all comer):
  - …
  - …
- Study Part 2 / MTD expansion (sqNSCLC + BC):

  …

  …

*Optional biopsy: Only for subjects who agreed on biopsy both at screening and on Cycle 2, Day 1.

Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C ~~or~~ nitrosoureas should not be given within 6 weeks of pre-treatment biopsy.

Tumor response evaluation **…**

…

New text:

…

Biomarker analysis in blood (serum) samples

Blood (serum) samples for the quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected as follows:

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

  …

  …

  Cycle 2-12: Days 1, 8, 15

  Cycles ≥13 Days 1 and 11

  EOT visit

- Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)

  - …
  - …
  - …
  - *Blood collection before administration of morning dose only for Cycle 1 of Part 1 and Part 2.

Biomarker analysis in TUMOR TISSUE

Biomarker analysis will be done at pre-screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN) according to FGFR expression levels / FGFR mutation using either an archival tumor tissue specimen or fresh tumor biopsy material (see Section 5.1.1: Inclusion criteria, and Section 7.4.4.1: Predictive marker investigation). **…**

- Study Part 1 / dose escalation (all comer):

  - …
  - …

- Study Part 1 / MTD expansion (all comer):

  …

  …

- Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN):
  - …
  - …

*Optional biopsy: Only for subjects who agreed on biopsy both at screening and on Cycle 2, Day 1.

Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

The evaluation of FGFR pathway mutations is planned retrospectively for subject in the MTD expansion cohorts.

Tumor response evaluation **…**

…

Section 7.4.4.1: Predictive marker investigations

This section was changed as a result of Modifications 1 and 2.

Old text:

Prediction Biomarker:

For subjects to be enrolled in study Part 1 / MTD expansion (all comer) and subjects to be enrolled in Study Part 2 / MTD expansion (sqNSCLC + BC) biomarker analysis will be done prior study start (subject stratification) on either a fresh or archival tumor biopsy sample to confirm high fibroblast growth factor receptor (FGFR) expression levels ~~and the presence or absence of additional genetic alterations in the FGFR signaling pathway~~ (see Section 5.1.1: Inclusion criteria).

Rationale for the quantification of tumor FGFR-1 -2- and -3 levels ~~by RNA in situ hybridization~~

Amplification of the FGFR1 8p12 gene locus has been observed in up to 20 % of sqNSCLC subjects (8)(9)(11). FGFR1 gene amplification is so far ~~the~~ one of the most frequently observed molecular alteration in sqNSCLC (30). Mutations in FGFR-encoding genes are rare in sqNSCLC subjects (< 2 %), whereas in bladder cancer, up to 70 % of all cases reveal mutations within FGFR3 gene (31). **…**

…

… In house data revealed that the best correlation with anti-tumor efficacy upon BAY1163877-treatment in preclinical cancer models was observed for total-FGFR mRNA tumor expression levels - including lung and bladder cancer models. **…**

... We therefore consider to stratify sqNSCLC and ~~bladder cancer~~ subjects to be enrolled in study Part 2 / MTD expansion by the quantification of total FGFR mRNA expression

levels in archival tissue samples ~~using RNA in situ hybridization~~ to exclude subjects that are unlikely to benefit from BAY1163877 therapy due to low overall FGFR target expression levels.

Rationale for the detection of genetic alterations in FGFR encoding genes and in FGFR pathway downstream signaling molecules

In subjects included in study Part 2 / MTD expansion (sqNSCLC + BC), genetic testing of tumor tissue may be necessary if a subject lacks a treatment response to BAY1163877 despite FGFR overexpression in tumor ~~-as revealed by RNA in situ hybridization.~~

…

Existence of such FGFR downstream pathway activating mutations in the case of lack of response to BAY1163877 treatment - despite high total FGFR mRNA tumor expression levels - should be evaluated retrospectively in subjects ~~to be~~ enrolled in study Part 2 / MTD expansion (sqNSCLC + BC).

…

We therefore consider genetic testing for FGFR3-activating mutations in bladder cancer subjects prior to treatment start - in case they lack high FGFR mRNA expression levels in tumor ~~as revealed by RNA in situ hybdridization.~~

~~For both investigations, DNA can be isolated from either tumor biopsy samples of archival tissue samples derived thereof.~~

New text:

Prediction Biomarker:

For subjects to be enrolled in study Part 1 / MTD expansion (all comer) and subjects to be enrolled in Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) biomarker analysis will be done prior study start (subject stratification) on either a fresh or archival tumor biopsy sample to confirm high fibroblast growth factor receptor (FGFR) expression levels / FGFR mutation (see Section 5.1.1: Inclusion criteria).

Rationale for the quantification of tumor FGFR-1 -2- and -3 levels

Amplification of the FGFR1 8p12 gene locus has been observed in up to 20 % of sqNSCLC subjects (8)(9)(11). FGFR1 gene amplification is so far one of the most frequently observed molecular alteration in sqNSCLC (30). In SCCHN, the FGFR1 gene was amplified in about 15 % of all cases (38). *In vitro* experiments with BAY 1163877 and published data with competitor compounds revealed equal sensitivity to proliferation inhibition by either adenocarcinoma or squamous subtype-derived lung cancer cell lines. In- house quantification of FGFR1-3 mRNA expression levels in patient-derived lung cancer tumors revealed a high FGFR1, 2 or 3 mRNA expression levels also in cases of lung adenocarinomas. In line with this, a recent publication confirmed a strong expression of FGFR1 mRNA also in adenocarcinoma biopsy samples in the absence of FGFR1 amplification (39). Therefore, we suggest to include lung adenocarcinoma patients into Part 2 of the study. Mutations in FGFR-encoding genes are rare in sqNSCLC subjects (< 2

%), whereas in bladder cancer, up to 70 % of all cases reveal mutations within FGFR3 gene (31). **…**

…

… In house data revealed that the best correlation with anti-tumor efficacy upon BAY1163877-treatment in preclinical cancer models was observed for total-FGFR mRNA tumor expression levels - including lung and bladder cancer models, and head and neck squamous cell cancer models. **…**

... We therefore consider to stratify sqNSCLC, LAC, BC and SCCHN subjects to be enrolled in study Part 2 / MTD expansion by the quantification of total FGFR mRNA expression levels in archival tissue samples in order to exclude subjects that are unlikely to benefit from BAY1163877 therapy due to low overall FGFR target expression levels.

Rationale for the detection of genetic alterations in FGFR encoding genes and in FGFR pathway downstream signaling molecules

In subjects included in study Part 1 / MTD expansion (all comer) and Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN), genetic testing of tumor tissue may be necessary if a subject lacks a treatment response to BAY1163877 despite FGFR overexpression in tumor.

…

Existence of such FGFR downstream pathway activating mutations in the case of lack of response to BAY1163877 treatment - despite high total FGFR mRNA tumor expression levels - should be evaluated retrospectively in subjects enrolled in study Part 1 / MTD expansion (all comer) and Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN).

…

We therefore consider genetic testing for FGFR3-activating mutations in bladder cancer subjects prior to treatment start - in case they lack high FGFR mRNA expression levels in tumor.

Section 7.5.1.3: Assessments and documentation of adverse events

This section was changed as a result of Modifications 2 and 10.

Old text:

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the subject, will be documented ~~in the subject's eCRF~~. AEs will be documented event based (using the CTCAE v4.03 guidelines). The observation phase for AEs will start with signing the Informed Consent and will end in general with the last visit of follow-up. Adverse events should be collected past 30 days after the study treatment stop for all AEs that were ongoing at the end of treatment as well as new SAEs (information may be obtained via phone call). The investigator is responsible for the grading of each category mentioned in Section 7.5.1.2.

…

If any subject dies within 30 days of last dose of study drug, the investigator will inform the sponsor and record the cause of death in detail within 24 hours on a SAE form.

…

New text:

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the subject, will be documented (see Section 9.1 for details). AEs will be documented event based (using the CTCAE v4.03 guidelines). The observation phase for AEs will start with signing the first Informed Consent and will end in general with the last visit of follow-up. Adverse events should be collected past 30-35 days after the study treatment stop for all AEs that were ongoing at the end of treatment as well as new SAEs (information may be obtained via phone call). The investigator is responsible for the grading of each category mentioned in Section 7.5.1.2.

…

If any subject dies within 30-35 days of last dose of study drug, the investigator will inform the sponsor and record the cause of death in detail within 24 hours on a SAE form.

…

Section 7.5.3.4: Electrocardiogram (ECG) - amended

This section was changed as a result of Modification 4.

Old text:

…

12-lead ECG readings will be performed in the supine position at the following time points:

- …
- Cycle 1, Day -3 and Day -2 (triplicate ECG readings) ["tablet bridging cohort" only]
- …

New text:

…

12-lead ECG readings will be performed in the supine position at the following time points:

- …
- Cycle 1, Day -3 and Day -2 (triplicate ECG readings) ["tablet bridging cohort" and "food effect assessment" only]

…

Section 7.5.4.2: Laboratory examinations

This section was changed as a result of Modification 2.

Old text:

…

Detailed information about the handling and labeling of the samples will be provided ~~separately in the~~ Laboratory Manual.

…

Tumor biopsies:

- Quantification of tumor p-ERK levels pre- and post-treatment by immunohistochemistry
  In this clinical trial, tumor biopsies will be examined using immunohistochemistry in order to examine the relationship between tumor p-ERK and response to BAY 1163877 therapy. Paired tumor biopsies should be obtained prior to study ~~entry (screening)~~ and on Cycle 2, Day 1 (at the end of Cycle 1) for analysis of p-ERK in tumor tissue.
- Quantification of tumor FGFR1,2 and 3 levels ~~by RNA in situ hybridization~~
  In this clinical trial tumor biopsies will be examined for FGFR1, FGFR2 and FGFR3 mRNA levels ~~using RNA in situ hybridization~~ from biopsy samples/ archival biopsy samples.
- ~~E~~valuation of mutations in either FGFR encoding genes or in FGFR downstream pathway genes ~~by PCR using Qiagen FGFR pathway mutation kit and genomic DNA~~ from biopsy samples / archival tissue samples.

…

New text:

…

Detailed information about the handling and labeling of the samples will be provided in a separate document (e.g. Laboratory Manual).

…

Tumor biopsies:

- Quantification of tumor p-ERK levels pre- and post-treatment by immunohistochemistry
  In this clinical trial, tumor biopsies will be examined using immunohistochemistry in order to examine the relationship between tumor p-ERK and response to BAY 1163877 therapy. Paired tumor biopsies should be obtained prior to study treatment and on Cycle 2, Day 1 (at the end of Cycle 1) for analysis of p-ERK in

tumor tissue.

- Quantification of tumor FGFR1,2 and 3 mRNA levels
  In this clinical trial tumor biopsies will be examined for FGFR1, FGFR2 and FGFR3 mRNA levels from biopsy samples/ archival biopsy samples.
- Retrospective evaluation of mutations in either FGFR encoding genes or in FGFR downstream pathway genes from biopsy samples / archival tissue samples.

…

Section 7.6.1: Diary

This section was changed as a result of Modification 10.

Old text:

…

The daily records of study drug intake will be transferred to the database.

…

New text:

…

The daily records of study drug intake will be transferred to the database in accordance with the data entry guidelines.

…

Section 8.4.5: Pharmacokinetic data - amended

This section was changed as a result of Modifications 4 and 5.

Old text:

…

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 treatment using both linear and semilogarithmic scale.

Pharmacokinetic characteristics (t_{max} and 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.

…

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

New text:

…

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 treatment 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} and 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. Amount and percent of drug excreted in urine will be described by arithmetic statistics, minimum, maximum and median.

…

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

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

be calculated by retransformation of the logarithmic data using the intra-individual standard deviation of the ANOVA.

Section 8.6: Further analysis described and reported under separate cover

This section was changed as a result of Modification 6.

Old text:

Not applicable (new section).

New text:

In order to evaluate the exposure-response during 4 cycles, two blood samples will be collected on Day 1 of Cycles 2-5, one before and one after a supervised dose. The resulting longitudinal exposure data will be modelled together with occurrences of selected adverse events and documented clinical responses. Also longitudinally measured PD biomarkers will be modelled with this exposure data. Exposure-response models and simulations after alternative dosing schedules will be reported in a separate document.

Section 9.1: Data recording

This section was changed as a result of Modifications 2 and 10.

Old text:

~~Entries made in the eCRF must be either verifiable against source documents, or have been directly entered into the eCRF, in which case the entry in the eCRF will be considered as the source data.~~

A Source Document Checklist will be used at site to identify the source data for all points collected.

…

- Results from pharmacokinetic analyses

The results of drug concentration measurements will be provided as electronic data files and transferred to Data Management, where the information necessary for evaluation will be added (e.g. administration and sampling time points, demographic data). This data set will be evaluated by the responsible pharmacokineticist. The complete pharmacokinetic evaluation will then be retransferred to Data Management.

- Data recorded from “only screened subjects (screening failures)”

For screening failures, …

New text:

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the study site. Entries into the eCRF should be made as soon as possible.

A Source Document Checklist will be used at site to identify the source data for all points collected.

…

- Results from pharmacokinetic analyses

The results of drug concentration measurements will be provided as electronic data files and transferred to Data Management, where the information necessary for evaluation will be added (e.g. administration and sampling time points, demographic data). This data set will be evaluated by the responsible pharmacokineticist. The complete pharmacokinetic evaluation will then be retransferred to Data Management.

Results from biomarker analyses

The results of biomarker analyses will be provided by the laboratories as electronic data files and transferred to Data Management, where the data is mapped into the database.

Results from ECG measurement

A part of the ECG analyses will be performed by Nabios. Nabios will send the electronic data files to Data Management, where the data is mapped into the database.

- Data recorded during the FGFR expression / FGFR mutation testing period (MTD expansion cohorts only)

Limited data will be recorded for all subjects in the FGFR expression / FGFR mutation testing period as described below:

- Subject number
- Demographic data
- Cancer classification including primary diagnosis (all comer for study Part 1; sqNSCLC, LAC, BC or SCCHN for Part 2), complete medical / oncological history data and TNM classification
- Life expectancy
- ECOG Performance Status
- Information on existence of an archival tumor biopsy specimen
- Details on collection of fresh tumor material (if applicable)
- Adverse events(s)

- Data recorded from “only screened subjects (screening failures)” including pre-screening

For screening failures, …

Section 11.2: Subject information and consent

This section was changed as a result of Modifications 1 and 2.

Old text:

All relevant information on the study will be summarized in ~~an~~ integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample form is provided as a document separate to this protocol.

Based on ~~this~~ subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject prior to his / her entry into the study

…

Only if the subject voluntarily agrees to sign the informed consent form and has done so, may he / she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the ISF or, if locally required, in the subject's note / file of the medical institution.

…

The informed consent form and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his / her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC / IRB's approval / favorable opinion in advance of use

New text:

All relevant information on the study will be summarized in 2 separate integrated subject information sheet and informed consent forms (SIS / ICFs) provided by the sponsor or the study center.

SIS / ICF for FGFR expression / FGFR mutation testing

For subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN), a separate SIS / ICF will be provided to subjects for FGFR expression / FGFR mutation testing. This separate SIS / ICF gives brief information on the study conduct, details on the tissue sample required to be taken to perform the tests along with information on possible risks.

SIS / ICF for study treatment eligibility

All subjects who have interest to participate in this study (including those who are confirmed presenting the appropriate FGF receptor level, or - for bladder cancer subjects -

who are confirmed carrying the FGFR mutation) will be provided the SIS / ICF for screening of study treatment eligibility no longer than 28 days prior to start of study treatment.

Samples of the 2 SIS /ICFs are provided as a document separate to this protocol.

Based on the subject information sheet(s), the investigator or designee will explain all relevant aspects of the study to each subject prior to his / her entry into the study

…

Only if the subject voluntarily agrees to sign the informed consent form(s) and has done so, may he / she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form(s). The subject will receive a copy of the signed and dated form(s).

The signed informed consent statement(s) is (are) to remain in the ISF or, if locally required, in the subject's note / file of the medical institution.

...

The informed consent form(s) and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form(s). The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his / her participation in the study by signing the revised informed consent form(s). Any revised written informed consent form and written information must receive the IEC / IRB's approval / favorable opinion in advance of use.

Section 12: Reference list

This section was changed as a result of Modifications 1 and 10.

Old text:

…

(36) Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. ~~(1982)~~ Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649-55

(37) Tibaldi F, Beck B, Bedding A ~~(2008)~~. Implementation of a Phase 1 Adaptive Clinical Trial in a Treatment of Type 2 Diabetes. Drug Information Journal: 42(05)

New text:

…

(36) Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology

Group. Am J Clin Oncol. 1982; 5: 649-55

(37) Tibaldi F, Beck B, Bedding A. Implementation of a Phase 1 Adaptive Clinical Trial in a Treatment of Type 2 Diabetes. Drug Information Journal. 2008; 42(05):455-465

(38) von Mässenhausen A, Franzen A, Heasley LE, Perner S. FGFR1 as a novel prognostic and predictive biomarker in squamous cell cancers of the lung and the head and neck area. Ann Transl Med. 2013;1(3). doi: 10.3978/j.issn.2305-5839.2013.06.08

(38) Wynes MW, Hinz TK, Gao D, Martini M, Marek LA, Ware KE, Edwards MG, Böhm D, Perner S, Helfrich BA, Dziadziuszko R, Jassem J, Wojtylak S, Sejda A, Gozgit JM, Bunn PA Jr, Camidge DR, Tan AC, Hirsch FR, Heasley LE. FGFR1 mRNA and protein expression, not gene copy number, predict FGFR TKI sensitivity acroll all lung cancer histologies. Clin Cancer Res, 2014 April 25 [Epup ahead of print] doi: 10.1158/1078-0432.CCR-13-3060

Section 14.1: Study flow chart - amended

This section was changed as a result of Modifications 1, 2, 4-6, 8, 9 and 10.

Old text:

Table 14-1: Study flow chart: ~~Screening~~ – Study Part 1 and Part 2

Measures / actions	Screening	
	Within 28 Days* before first study drug administration	Within 7 Days* before first study drug administration
Signed informed consent[(A)]	X	
Inclusion / exclusion criteria	X	X
Demographic data	X	
Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report	X	
Complete medical / oncological history	X	
TNM classification	X	
Concomitant diseases, NYHA grading	X	
Review of baseline toxicities	X	X
Baseline characteristics (smoking habits / history, alcohol consumption)	X	
Previous therapy	X	
Concomitant therapy	X	X
Physical examination	X	
Body height		X
Body weight / calculation of BMI[(B)]		X
Vital signs[(C)]		X
ECOG performance status	X	
12-lead ECG[(D)]	X	
Echocardiography or MUGA scan		X
Obtain pre-treatment biopsy[(E)]	X	
Stratification of subjects to be enrolled in MTD expansion cohorts (Part 1 and Part 2)[(F)]	X	
Blood / urine collection for safety lab tests[(G)]		X
Blood (serum) samples collection for biomarker investigations[(H)]		X
Only females: Urine pregnancy test		X
Calculation of eGFR[(I)]		X
Ophthalmological examination at consultant	X	
CT / MRI scans	X	

Table 14-1: Study flow chart: ~~Screening~~ – Study Part 1 and Part 2

Documentation of lesion(s) according to RECIST v1.1		**X**
Adverse events(J)		**X**

*Pre-study examinations may require hospitalization for 1- 2 days.

~~(A)~~ Informed consent can be signed before 28-day screening phase.

(B) **…**

(C) **...**

(D) **...**

(E) A pre-treatment biopsy at screening will be obtained from all subjects who agreed on this. The biopsy sample will be sent to laboratory for biomarker evaluation, see Table 14–5, Table 14–6 and Table 14–7.

~~A pre-treatment biopsy is optional …~~

~~…for subjects in study Part 1 / dose-escalation (all comer).~~

~~…for subjects in study Part 2 / MTD expansion (sqNSCLC + BC) for whom an archival biopsy is available.~~

~~A pre-treatment biopsy is mandatory …~~

~~…for subjects in study Part 1 / MTD expansion (all comer).~~

~~…for subjects in study Part 2 / MTD expansion (sqNSCLC + BC) who have no archival biopsy.~~

~~Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C or nitrosoureas should not be given within 6 weeks of pre-treatment biopsy.~~

(F) ~~Obtain archival tissue samples for stratification of subjects participating in the MTD expansion cohorts of study Part 1 (all comer) and study Part 2 (sqNSCLC + BC),~~ see Table 14–6 and Table 14–7. ~~If no archival material is available, fresh tumor biopsy material is required for stratification (see E: mandatory biopsy).~~

(G) Safety lab tests: see Table 14–4

(H) **...**

(I) **...**

(J) **...**

Table 13–3: Study flow chart: Treatment (Cycle 1, Day -3 to Day -1) – Study Part 1 and Part 2

Measures / actions	**TREATMENT (only for "tablet bridging cohort")**		
	Cycle 1		
	Day -3	Day -2	Day -1
…	…	…	…
…	…	…	…
…	…	…	…
…	…		…
…	…	…	…
…	…	…	…
…	…	…	…
…	…	…	…
…	…		
…	…		
PK blood sampling(F)	…		
Administration of BAY 1163877 tablet (single dose)(G)	…		
…	…	…	…

(A) …

(B) …

(C) …

(D) …

(E) …

(F) PK sampling will be done as follows (for details see Laboratory Manual):

– …

(G) Oral administration of BAY 1163877 tablet formulation on Cycle 1, Day -3 will be done by a member of the site.

Table 14-3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1 and Part 2

Measures / actions	TREATMENT									FOLLOW-UP
	Cycle 1 (21 days)					~~Cycle≥2~~ (21 days)			EOT Visit Within ~~7~~-14 days after last dose	FU-Visit / Phone Call[A] At 30-35 days after last dose
Day (D)	D1	D2	D3	D8 ±1	D15	D1	D8 ±1	D15 ±1		
Concomitant medication	…	…	…	…	…	…	…	…	…	…
Physical examination	…	…	…	…	…	…	…	…	…	…
Ask subject for changes in vision[B]	…	…	…	…	…	…	…	…	…	…
Cardiovascular assessment[C]	…		…	…	…	…	…	…	…	…
Body temperature	…	…	…	…	…	…			…	
Body weight	…								…	
12-lead ECG readings[D]	…	…			…	…			…	
ECOG performance status	…	…	…	…	…	…	…	…	…	
Blood / urine collection for safety lab tests[E]	…			…	…	…	…	…	…	
Calculation of eGFR[F]	…			…	…	…	…	…	…	
Blood (serum) samples collection for biomarker investigations[G]	…		…	…	…	…	…	…	…	
Obtain tumor biopsy for biomarker tests[H]						…				
PK blood sampling[I]	…				…					
Ophthalmological examination						…			…	
CT / MRI scans and documentation of response according to RECIST v1.1						…				
Dispense / return of BAY 1163877 and diary~~[J]~~	…		…	…	…	…	…	…	…	

Continued

Table 14–3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1 and Part 2 (Continued)

Measures / actions	TREATMENT			FOLLOW-UP
	Cycle 1 (21 days)	~~Cycle≥2~~ (21 days)	EOT Visit Within	FU-Visit / Phone Call[A]

Table 14–3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1 and Part 2 (Continued)

									~~7~~-14 days after last dose	**At 30-35 days after last dose**
Day (D)	D1	D2	D3	D8 ±1	D15	D1	D8 ±1	D15 ±1		
Administration of BAY 1163877 if PK assessment (~~K~~)	…		…							
Administration of BAY 1163877 if no PK assessment(~~L~~)	…									
Toxicities / AE assessment	…	…	…	…	…	…	…	…	…	…

…

(A) …

(B) …

(C) …

(D) …

(E) …

(F) …

(G) …

(H) …

A biopsy on Cycle 2, Day 1 is optional …
….
…for subjects in study Part 2 / MTD expansion (sqNSCLC + BC).
….

Continued

Table 14–3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1 and Part 2 (Continued)

(I)	**…**
~~(J)~~	First oral administration of BAY 1163877 on Cycle 1 Day 1 will be done **…**
~~(K)~~	Subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects of study Part 2) will receive a single-dose of BAY 1163877 on Cycle 1, Day 1 (morning), followed by a “drug-free day” (to enable single dose PK assessments).Treatment with BAY 1163877 will resume **...**
~~(L)~~	Subjects without PK assessment in study Part 2 **…**

New text

Table 14-1: Study flow chart: Pre-Treatment – Study Part 1 and Part 2 - amended

Measures / actions	FGFR expression / FGFR mutation testing Only for subjects recruited for MTD expansion cohorts (Part 1 and Part 2)	Screening Within 28 Days* before first study drug administration	Screening Within 7 Days* before first study drug administration
Signed informed consent	X(A1)	X(A2)	
Limited inclusion criteria	X		
Inclusion / exclusion criteria		X	X
Demographic data	X(K)	X(K)	
Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report	X(K)	X(K)	
Complete medical / oncological history	X(K)	X(K)	
TNM classification	X(K)	X(K)	
Concomitant diseases, NYHA grading		X	
Review of baseline toxicities	X	X	X
Baseline characteristics (smoking habits / history, alcohol consumption)		X	
Previous therapy		X	
Concomitant therapy		X	X
Physical examination		X	
Body height			X
Body weight / calculation of BMI(B)			X
Vital signs(C)			X
ECOG performance status	X	X	
12-lead ECG(D)		X	
Echocardiography or MUGA scan			X
Obtain pre-treatment biopsy(E)		X	
Obtain archival tissue sample or fresh tumor material for FGFR expression / FGFR mutation testing	X		

Continued

Table 14-1: Study flow chart: Pre-Treatment – Study Part 1 and Part 2 - amended (Continued)

Measures / actions	FGFR expression / FGFR mutation testing Only for subjects recruited for MTD expansion cohorts (Part 1 and Part 2)	Screening Within 28 Days*	Screening Within 7 Days* before first study drug administration
Stratification of subjects to be enrolled in MTD expansion cohorts (Part 1 and Part 2)(F)	X		
Blood / urine collection for safety lab tests(G)		X	X
Blood (serum) samples collection for biomarker investigations(H)			X
Only females: Urine pregnancy test			X
Calculation of eGFR(I)			X
Ophthalmological examination at consultant		X	
CT / MRI scans		X	
Documentation of lesion(s) according to RECIST v1.1			X
Adverse events(J)	X	X	X

*Pre-study examinations may require hospitalization for 1- 2 days.

(A1) Informed consent for FGFR expression / FGFR mutation testing

(A2) Informed consent for study treatment eligibility can be signed before 28-day screening phase.

(B) **…**

(C) **...**

(D) **...**

(E) A pre-treatment biopsy at screening will be obtained from all subjects who agreed on this. The biopsy sample will be sent to laboratory for biomarker evaluation, see Table 14–5, Table 14–6 and Table 14–7.

(F) For details, see Table 14–6 and Table 14–7.

(G) Safety lab tests: Virology tests within 28 days before first study drug administration, all other blood and urine tests within 7 days before first study drug administration, for details see Table 14–4.

(H) **…**

(I) **…**

Continued

Table 14–1: Study flow chart: Pre-Treatment – Study Part 1 and Part 2 - amended (Continued)

(J)	…
(K)	Documentation has not to be provided twice for subjects enrolled in the MTD expansion cohorts.

Table 14–2: Study flow chart: Treatment (Cycle 1, Day -3 to Day -1) – Study Part 1 and Part 2 - amended

Measures / actions	**TREATMENT (only for "tablet bridging cohort" (Part 1) and for "food effect assessment" (Part 1 and Part 2))**		
	Cycle 1		
	Day -3	Day -2	Day -1
…	…	…	…
…	…	…	…
…	…	…	…
…	…		…
…	…	…	…
…	…	…	…
…	…	…	…
…	…	…	…
…	…		
…	…		
PK blood sampling(F)	…		
Administration of BAY 1163877 (single dose) after a high-fat, high-calorie breakfast(G)	**X**		
Administration of BAY 1163877 tablet (single dose)(H)	…		
…	…	…	…

(A) …

(B) …

(C) …

(D) …

(E) …

(F) PK sampling will be done as follows (for details see separate document e.g. Laboratory Manual):

– …

(G) *Only for subjects with "food effect assessment" in Part 1 and Part 2:* Oral administration of a single dose of BAY 1163877 immediately (within 5 minutes) after consumption of a high-fat, high-calorie breakfast (supervised by a member of the site), see Section 6.4.2.2.1.

(H) *Only for subjects included in the "tablet bridging cohort" of Part 1 / dose escalation:* Oral administration of BAY 1163877 tablet formulation on Cycle 1, Day -3 will be done by a member of the site.

Continued

Table 14–3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1 and Part 2 - amended

Measures / actions	TREATMENT											FOLLOW-UP
	Cycle 1 (21 days)					Cycles 2-12 (21 days)			Cycles ≥13 (21 days)		EOT Visit Within 0-14 days after last dose	FU-Visit / Phone Call[A] At 30-35 days after last dose
Day (D)	D1	D2	D3	D8 ±1	D15	D1	D8 ±1	D15 ±1	D1	D11		
Concomitant medication	…	…	…	…	…	…	…	…	X	X	…	
Physical examination	…	…	…	…	…	…	…	…	X	X	…	…
Ask subject for changes in vision[B]	…	…	…	…	…	…	…	…	X	X	…	…
Cardiovascular assessment[C]	…		…	…	…	…	…	…	X	X	…	…
Body temperature	…	…	…	…	…	…			X		…	
Body weight	…					X			X		…	
12-lead ECG readings[D]	…	…			…	…			X		…	
ECOG performance status	…	…	…	…	…	…	…	…	X	X	…	
Blood / urine collection for safety lab tests[E]	…			…	…	…	…	…	X	X	…	
Calculation of eGFR[F]	…			…	…	…	…	…	X	X	…	
Blood (serum) samples collection for biomarker investigations[G]	…		…	…	…	…	…	…	X	X	…	
24-hour urine collection[N]	X		…	…								
Obtain tumor biopsy for biomarker tests[H]						X (Cycle 2 only)						
PK blood sampling[I]	…				…							
PK blood sampling for PK / PD modeling[J]						X						
Ophthalmological examination						Every 2nd cycle					…	
CT / MRI scans and documentation of response according to RECIST v1.1						End of Cycle 2, then after every 3rd cycle						
Dispense / return of BAY 1163877 and diary[K]	…		…	…	…	…	…	…	X	X	…	

Continued

Table 14–3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1 and Part 2 – amended (Continued)

Measures / actions	**TREATMENT**											**FOLLOW-UP**
	Cycle 1 (21 days)					**Cycles 2-12 (21 days)**			**Cycles ≥13 (21 days)**		**EOT Visit Within 0-14 days after last dose**	**FU-Visit / Phone Call(A) At 30-35 days after last dose**
Day (D)	D1	D2	D3	D8 ±1	D15	D1	D8 ±1	D15 ±1	D1	D11		
Administration of BAY 1163877 if PK assessment(L)	…		**Continuous, twice-daily administration**									
Administration of BAY 1163877 if no PK assessment(M)	**Continuous, twice-daily administration**											
Toxicities / AE assessment	…	…	…	…	…	…	…	…	X	X	…	…

……

(A) **...**

(B) **…**

(C) **…**

(D) **…**

(E) **…**

(F) **…**

(G) **...**

(H) **...**

A biopsy on Cycle 2, Day 1 is optional …
….
…for subjects in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN).

(I) **...** (J) All subjects participating in the MTD expansion cohorts (Part 1 or Part 2) 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

Table 14–3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1 and Part 2 – amended (Continued)

post-dose). The dose needs to be taken under supervision and the time recorded.
(K) First oral administration of BAY 1163877 on Cycle 1 Day 1 will be done **…**
(L) Subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects of study Part 2) will receive a single-dose of BAY 1163877 on Cycle 1, Day 1 (morning), followed by a "drug-free day" (to enable single dose PK assessments). Subjects with "food effect assessment" in Part 1 and Part 2 take the morning dose after an overnight fast of at least 8 hours (see Section 6.4.2.2.1). Treatment with BAY 1163877 will resume **...**
(M) Subjects without PK assessment in study Part 2 **…**
(N) In approximately 8 subjects enrolled in MTD expansion cohorts (study Part 1 and Part 2), urine will be collected for 24 hours after dosing.

Section 14.2: Laboratory examinations - amended

This section was changed as a result of Modifications 1-3, 8 and 10.

Old text:

Table14-4: Parameters and time points of laboratory examinations performed at local laboratory or study site (safety laboratory) – Study Part 1 and Part 2 - amended

Parameters	~~Screening~~	Treatment				Follow-up	
		Cycle 1 Day -3	~~Each Cycle~~ Day 1	Day 8	Day 15	EOT visit	FU visit
BLOOD							
Hematology: …	…	…	…	…	…	…	…
Coagulation: …	…	…	…	…	…	…	…
Biochemistry: …	…	…	…	…	…	…	…
Virology: …	…						
URINE							
Macroanalysis: …	…	…	…	…	…	…	…
Urinalysis (dip stick): …	…	…	…	…	…	…	…
Laboratory analysis[C]: …	…	…	…	…	…	…	…
Microscopic urinalysis[D]: …	…	…	…	…	…	…	…
Pregnancy test[F]	…						
…							

Table14-5: Parameters and time points for biomarker investigations in study Part 1 / dose escalation (all comer)

Parameters	Screening	Treatment							Follow-up EOT visit
TUMOR TISSUE:		**~~Cycle 2, Day 1~~**							
…	…	…							
		Cycle 1				**~~Cycle ≥2~~**			
Blood (serum) samples***:**		~~D1~~	~~D3~~	~~D8~~	~~D15~~	~~D1~~	~~D8~~	~~D15~~	
…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…

~~D = day~~

…

…

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877.

(A) … Mitomycin C, ~~or~~ nitrosoureas should not be given within 6 weeks of pre-treatment biopsy.

(B) …

…

Table 14–6: Parameters and time points for biomarker investigations in study Part 1 / MTD expansion (all comer)

Parameters	Screening	Treatment							Follow-up EOT visit
TUMOR TISSUE:		~~**Cycle 2, Day 1**~~							
…	…	…							
FGFR1/2/3 expression	~~X~~[(C)]								
FGFR and FGFR pathway mutations	~~X~~[(C)]								
		Cycle 1				~~**Cycle ≥2**~~			
Blood (serum) samples*:		~~D1~~	~~D3~~	~~D8~~	~~D15~~	~~D1~~	~~D8~~	~~D15~~	
…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…

~~D = day~~

…

…

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877.

(A) ~~A pre-treatment biopsy (e.g. endoscopic or ultrasound-guided biopsy) must be obtained at screening (~~mandatory biopsy ~~within 28 days prior to start of treatment).~~
Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C ~~or~~ nitrosoureas should not be given within 6 weeks of pre-treatment biopsy.

(B) …

(C) An archival tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels ~~and evaluation of FGFR mutations~~ necessary for subject stratification (see Section 5.1.1: Inclusion criteria). If no archival biopsy sample is available ~~the biopsy sample from the mandatory pre-treatment biopsy at screening may be used for subject stratification. Additionally isolated tumor DNA, if available, can be requested for genetic testing.~~

Table 14–7: Parameters and time points for biomarker investigations in study Part 2 / MTD expansion (sqNSCLC + BC)

Parameters	Screening	Treatment			Follow-up EOT visit
TUMOR TISSUE:		~~**Cycle 2, Day 1**~~			
…	…	…			
FGFR1/2/3 expression	~~X~~(C)				
FGFR and FGFR pathway mutations	~~X~~(C)				
		~~**Each Cycle**~~			
Blood (serum) samples*:		Day 1	Day 8	Day 15	
…	**…**	**…**	**…**	**…**	**…**
…	**…**	**…**	**…**	**…**	**…**

…

…

…

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877.

(A) A pre-treatment biopsy (e.g. endoscopic or ultrasound-guided biopsy) will be obtained at screening if the subject agreed on this. The pre-treatment biopsy is optional for subjects for whom an archival biopsy is available. ~~If no archival biopsy is available, the pre-treatment biopsy is mandatory, see C~~
Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C ~~or~~ nitrosoureas should not be given within 6 weeks of pre-treatment biopsy.

(B) **…**

(C) An archival tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels ~~and evaluation of FGFR mutations necessary for subject stratification~~ (see Section 5.1.1: Inclusion criteria). If no archival biopsy is available ~~generation of a pre-treatment biopsy at screening is mandatory for subject stratification, see (A). Additionally isolated tumor DNA, if available, can be requested for genetic testing.~~

…

New text:

Table 14-4: Parameters and time points of laboratory examinations performed at local laboratory or study site (safety laboratory) – Study Part 1 and Part 2 – amended

Parameters	PRE-TREATMENT		TREATMENT						FOLLOW-UP	
	FGFR expression / FGFR mutation testing	Screening	Cycle 1	Cycles 2-12			Cycle ≥13		EOT visit	FU visit
			Day -3	Day 1	Day 8	Day 15	Day 1	Day 11		
BLOOD										
Hematology: …		…	…	…	…	…	X	X	…	…
Coagulation: …		…	…	…	…	…	X	X	…	…
Biochemistry: …		…	…	…	…	…	X	X	…	…
Virology: …		…								
URINE										
Macroanalysis: …		…	…	…	…	…	X	X	…	…
Urinalysis (dip stick): …		…	…	…	…	…	X	X	…	…
Laboratory analysis[C]: …		…	…	…	…	…	X	X	…	…
Microscopic urinalysis[D]: …		…	…	…	…	…	X	X	…	…
Pregnancy test[F]		…								
…										

Table 14–5: Parameters and time points for biomarker investigations in study Part 1 / dose escalation (all comer) - amended

Parameters	PRE-TREATMENT		TREATMENT									FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycle 1 Day 1	Cycle 1 Day 3	Cycle 1 Day 8	Cycle 1 Day 15	Cycles 2-12 Day 1	Cycles 2-12 Day 8	Cycles 2-12 Day 15	Cycles ≥13 Day 1	Cycles ≥13 Day 11	EOT visit
Tumor tissue:												
p-ERK1/2 levels		…					X(B) only Cycle 2					
Blood (serum) samples*:												
FGF23		…	…	…	…	…	…	…	…	X	X	…
Phosphate, Calcium		…	…	…	…	…	…	…	…	X	X	…

…

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877 only for Cycle 1.

(A) … Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

(B) …

…

Table 14-6: Parameters and time points for biomarker investigations in study Part 1 / MTD expansion (all comer) - amended

Parameters	PRE-TREATMENT		TREATMENT									FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycle 1 Day 1	Cycle 1 Day 3	Cycle 1 Day 8	Cycle 1 Day 15	Cycles 2-12 Day 1	Cycles 2-12 Day 8	Cycles 2-12 Day 15	Cycles ≥13 Day 1	Cycles ≥13 Day 11	EOT visit
Tumor tissue:												
p-ERK1/2 levels		X(A)					X(B) only Cycle 2					
FGFR1/2/3 expression	X(C)											
FGFR and FGFR pathway mutations	X(C)											
Blood (serum) samples*:												
FGF23		…	…	…	…	…	…	…	…	X	X	…
Phosphate, Calcium		…	…	…	…	…	…	…	…	X	X	…

…
FGFR 1/2/3 = fibroblast growth factor receptor 1, 2 and 3

…

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877 only for Cycle 1.

(A) An additional biopsy is not requested if a biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit. Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

(B) …

(C) An archival or fresh tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels, necessary for subject stratification (see Section 5.1.1: Inclusion criteria). If no archival biopsy sample is available which has been handled and processed as described in the lab manual, collection of fresh tumor biopsy material is mandatory for stratification.
The evaluation of FGFR pathway mutations is planned retrospectively for all subjects.

Table 14-7: Parameters and time points for biomarker investigations in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) - amended

Parameters	PRE-TREATMENT		TREATMENT					FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycles 2-12			Cycles ≥13		EOT visit
			Day 1	Day 8	Day 15	Day 1	Day 11	
Tumor tissue:								
p-ERK1/2 levels		X(A)	X(B) only Cycle 2					
FGFR1/2/3 expression	X(C)							
FGFR and FGFR pathway mutations	X(C)							
Blood (serum) samples*:								
FGF23		…	…	…	…	X	X	…
Phosphate, calcium		…	…	…	…	X	X	…

…

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877 only for Cycle 1.

(A) A pre-treatment biopsy (e.g. endoscopic or ultrasound-guided biopsy) will be obtained at screening if the subject agreed on this. The pre-treatment biopsy is optional for subjects for whom an archival biopsy is available. An additional biopsy is not requested if a biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit.
Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

(B) …

(C) An archival tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels necessary for subject stratification (see Section 5.1.1: Inclusion criteria). If no archival biopsy is available which has been handled and processed as described in the lab manual, collection of fresh tumor biopsy material is mandatory for stratification.
Samples of BC subjects will also be tested on activating FGFR3 mutation status for stratification.
The evaluation of FGFR pathway mutations is planned retrospectively for all subjects.

p-ERK1/2 levels will only be analyzed if a subject is willing to undergo both a pre-treatment biopsy at screening and a second biopsy on Cycle 2, Day 1.

15.4 Amendment 4

Date of amendment: 31 Oct 2014

15.4.1 Overview of changes

Modification 1: Modification of the total number of subjects

Rationale for introducing Modification 1

Available data of the conducted study have revealed, that the total number of screening failures is larger than anticipated. Therefore an adaptation of the total number of subjects is necessary.

List of all CSP sections affected by Modification 1:

- Synopsis
- Section 4

Modification 2: Definition of the MTD

Rationale for introducing Modification 2

Preliminary data of the conducted study have revealed, that dose escalations without major toxicities could be carried out beyond the planned maximum dosage of 1100 mg/day. Therefore the decision to define the RP2D should be determined by PK and/or PD results.

List of all CSP sections affected by Modification 2:

- Synopsis
- Section 4

Modification 3: Minor corrections/inconsistencies

Rationale for introducing Modification 3

Minor text modifications and corrections of omissions or terminology were done for clarification and to ensure correct and consistent wording.

List of all CSP sections affected by Modification 3:

- Section 5.1.2.3
- Section 6.9.2
- Section 7.3.1
- Section 9.1

Modification 4: Assessment and recording of toxicity and AE in the FGFR

expression / FGFR mutation testing group (MTD expansion cohorts only)

Rationale for introducing Modification 4

Subjects without invasive procedure to obtain tumor material for testing of the FGFR expression pattern are no subject of toxicity / AE assessment and recording.

List of all CSP sections affected by Modification 4:

Section 7.1.2.1.1

Section 7.5.1.1

Section 7.5.1.3

Section 9.1

Table 14-1

Modification 5: Laboratory examinations for coagulation parameters, safety laboratory FU visit

Rationale for introducing Modification 5

Coagulation parameters will be determined for all subjects once per cycle. The FU visit will not cover safety laboratory parameter as described in section 7.1.2.3.4.

List of all CSP sections affected by Modification 5:

- Section 7.5.4.2
- Table 14-4

Modification 6: Biomarker investigations

Rationale for introducing Modification 6

Standardization of biomarker sampling in all MTD subjects.

List of all CSP sections affected by Modification 6:

- Section 7.1.2.3.1
- Section 7.4.4
- Table 14-6
- Table 14-7

15.4.2 Changes of protocol

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the “old

text" refers to the protocol version preceding this amendment. Deletions are crossed out in the "old text". Additions are underlined in the "new text". Corrections of typing errors, omissions or terminology (minor corrections) are not highlighted in this amendment.

Synopsis

This section was changed as a result of Modifications 1 and 2.

Old text:

Title	…
Short title	…
Clinical study phase	…
Project number	…
Study objective(s)	…
Test drug(s)	…
Name of active ingredient	…
Formulation IMP 1	…
Formulation IMP 2	…
Dose(s)	…
Route of administration	…
Duration of treatment	…
Reference drug (s)	…
Indication	…
Diagnosis and main criteria for inclusion	…
Study design	…
Methodology	…
Type of control	…

Number of subjects	~~Up to 111~~ subjects will be enrolled in the ~~screning~~ phase of the study. • *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. …
Primary variables	…

New text:

Title	**…**
Short title	**…**
Clinical study phase	**…**
Project number	**…**
Study objective(s)	**…**
Test drug(s)	**…**
Name of active ingredient	**…**
Formulation IMP 1	**…**
Formulation IMP 2	**…**
Dose(s)	**…**
Route of administration	**…**
Duration of treatment	**…**
Reference drug (s)	**…**
Indication	**…**

Diagnosis and main criteria for inclusion	**…**
Study design	…
Methodology	**…** **<u>Determination of the MTD:</u>** 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. 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. 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 drug safety monitoring team = 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 (see details in Section **16.4**).

Methodology (continued)	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. 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 patient will be made by the investigator according to the criteria specified in the protocol (Section 8.4). 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: …
Type of control	…

Number of subjects	Approximately 200 subjects will be enrolled in the pre-treatment phase of the study. • *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)*: 40 additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and a cohort of 20 evaluable subjects with BC or SCCHN treated at MTD (at least 8 subjects per indication).
Primary variables	…
Plan for statistical analysis	…

Section 4: Study design

This section was changed as a result of Modification 1.

Old text:

…

Planned sample size:

It is expected that ~~up to 111~~ subjects will be enrolled in the ~~screening~~ phase of the study and approximately 92 subjects will be enrolled in the treatment phase.

…

New text:

…

Planned sample size:

It is expected that approximately 200 subjects will be enrolled in the pre-treatment-phase of the study and approximately 92 subjects will be enrolled in the treatment phase.

…

Section 4: Study design

This section was changed as a result of Modification 2.

Old text:

...

Determination of the maximum tolerated dose (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.

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.

...

New text:

…

Determination of the maximum tolerated dose (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 (Section 8.4).

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.

...

Section 5.1.2.3: Exclusion criteria

This section was modified as a result of Modification 3.

Old text:

Medical and surgical history

- ...
- Unresolved toxicity higher than CTCAE v 4.03 Grade 1 (excluding alopecia ~~and~~ anemia) attributed to any prior therapy / procedure
- ...

New text:

Medical and surgical history

- ...
- Unresolved toxicity higher than CTCAE v 4.03 Grade 1 (excluding alopecia, anemia and / or hypothyroidism) attributed to any prior therapy / procedure
- ...

Section 6.9.2: Prohibited concomitant therapy

This section was modified as a result of Modification 3.

Old text:

Concomitant therapy with the following medication is NOT allowed:

- Systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors, hormonal therapy and experimental or approved therapies during this trial or within 30 days before starting to receive study medication
- Bone marrow transplant or stem cell rescue.
- ...

New text:

Section 6.9.2: Prohibited concomitant therapy

- Anticancer chemotherapy or immunotherapy during the study or within 5-half-lives prior to start of study treatment. Acute toxic effects of previous anticancer chemotherapy or immunotherapy have to be normalized completely (excluding alopecia, anemia and / or hypothyroidism). Anticancer therapy is defined as any agent or combination of agents with clinically proven anti-tumor activity administered by any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints.
- Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks before starting to receive study treatment or within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies in case of performed biopsy procedure

- Bone marrow transplant or stem cell rescue.
- ...

Section 7.1.2.1.1: FGFR expression / FGFR mutation testing (MTD expansion cohorts only)

This section was changed as a result of Modification 4.

Old text:

FGFR expression / FGFR mutation testing (MTD expansion cohorts only)

A separate subject information sheet / informed consent form (SIS / ICF) for FGFR expression / FGFR mutation testing must be signed by all subjects recruited for study Part 1 or Part 2 MTD expansion cohort (see Section 13.2).

The following activities / examinations will be performed prior to FGFR expression / FGFR mutation testing:

- ...
- Toxicity / AE assessment and recording

All subjects enrolled into the study will be listed on a subject enrollment log provided by the sponsor's representatives.

New text:

FGFR expression / FGFR mutation testing (MTD expansion cohorts only)

A separate subject information sheet / informed consent form (SIS / ICF) for FGFR expression / FGFR mutation testing must be signed by all subjects recruited for study Part 1 or Part 2 MTD expansion cohort (see Section 13.2).

The following activities / examinations will be performed prior to FGFR expression / FGFR mutation testing:

- ...
- Toxicity / AE assessment and recording only in case an invasive procedure will be performed to obtain tumor material after subjects´ informed consent

All subjects enrolled into the study will be listed on a subject enrollment log provided by the sponsor's representatives.

Section 7.1.2.3.1: Cycle 1

This section was changed as a result of Modification 6.

Old text:

Day 3

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature
- ECOG performance status
- *Only for subjects included in study Part 1 (all comer):* Blood (serum) samples collection for biomarker investigations, see Table 16-5 ~~and Table 16-6~~
- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2)
- …

New text:

Day 3

- Update of concomitant therapy
- Physical examination
- Ask subject for changes in vision
- Cardiovascular assessment (BP and HR)
- Measurement of body temperature
- ECOG performance status
- *Only for subjects included in study Part 1/ dose escalation (all comer):* Blood (serum) samples collection for biomarker investigations, see Table 16-5
- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2)
- …

Section 7.3.1: Tumor evaluation – response assessment (RECIST)

This section was changed as a result of Modification 6.

Old text:

In *measurable* lesions (i.e., at the primary site, visceral or nodal [in lymph nodes ≥ ~~2~~ cm] lesions), the objective response will be assessed by CT / MRI scan at the EOT visit and documented according to the revised RECIST guideline, Version 1.1 (RECIST, v1.1), see Section 16.8. The assessment will be done by the investigators. No central evaluation is planned for this study.

New text:

In *measurable* lesions (i.e., at the primary site, visceral or nodal [in lymph nodes ≥ 1,5 cm] lesions), the objective response will be assessed by CT / MRI scan at the EOT visit and documented according to the revised RECIST guideline, Version 1.1 (RECIST, v1.1), see Section 16.8. The assessment will be done by the investigators. No central evaluation is planned for this study.

Section 7.4.4: Biomarker investigations

This section was changed as a result of Modification 6.

Old text:

Biomarker analysis in blood (serum) samples

Blood (serum) samples for the quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected as follows:

- Study Part 1 / dose escalation ~~+ MTD expansion (all comer)~~
  - Screening
  - Cycle 1: Days 1*, 3*, 8*, and 15*
  - Cycles 2-12: Days 1, 8, 15
  - Cycles ≥13: Days 1 and 11
  - EOT visit
- Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)

  Screening

  ~~All Cycles: Days 1*, 8*, and 15*~~

  EOT visit

*Blood collection before administration of morning dose only for Cycle 1 of Part 1 and Part 2.

…

New text:

…

Biomarker analysis in blood (serum) samples

Blood (serum) samples for the quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected as follows:

- Study Part 1 / dose escalation
  - Screening
  - Cycle 1: Days 1*, 3*, 8*, and 15*
  - Cycles 2-12: Days 1, 8, 15
  - Cycles ≥13: Days 1 and 11
  - EOT visit
- Study Part 1 / MTD expansion (all comer) and Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)

  Screening

  Cycles 1-12: Days 1*, 8*, 15*

  Cycles ≥13: Days 1 and 11

  EOT visit

*Blood collection before administration of morning dose only for Cycle 1 of Part 1 and Part 2.

…

Section 7.5.1.1: Definitions

This section was changed as a result of Modification 4.

Old text:

…

Serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a) Results in death

b) Is life-threatening

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

c) Requires insubject hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned
  (i.e. elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE
  (e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependant on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Is a congenital anomaly / birth defect

Is another medically important serious event as judged by the investigator

New text:

…

Serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

Results in death

Is life-threatening

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

Requires insubject hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned
  (i.e. elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE
  (e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may

fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependant on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Is a congenital anomaly / birth defect

Is another medically important serious event as judged by the investigator

All SAEs occurring after the IC for study treatment eligibility has been obtained, until the end of the follow-up period must be handled via this process. All serious diagnoses, symptom(s), sign(s) or finding(s) that have a start date after signing the IC must be recorded as SAEs. This also includes all serious events with a start date during the pre-treatment period for subject stratification (FGFR expression / FGFR mutation testing period), **in case an invasive procedure was performed to obtain tumor material.** A condition that was present before signing the IC for study treatment eligibility and worsens after signing the IC must also be recorded as an SAE if the serious criteria are met.

Section 7.5.1.3: Assessments and documentation of adverse events

This section was changed as a result of Modification 4.

Old text:

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the subject, will be documented (see Section 11.1 for details). AEs will be documented event based (using the CTCAE v4.03 guidelines). The observation phase for AEs will start with signing the first Informed Consent and will end in general with the last visit of follow-up. Adverse events should be collected past 30-35 days after the study treatment stop for all AEs that were ongoing at the end of treatment as well as new SAEs (information may be obtained via phone call). The investigator is responsible for the grading of each category mentioned in Section **9.5.1.2**.

…

New text:

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the subject, will be documented (see Section 11.1 for details). AEs will be documented event based (using the CTCAE v4.03 guidelines). The observation phase for AEs will start with signing the first Informed Consent and will end in general with the last visit of follow-up. All AEs identified after first IC during the pre-treatment period for subject stratification (FGFR expression / FGFR mutation testing period) will not be documented in the eCRF, in case no invasive procedure will be

performed to obtain tumor material. Adverse events should be collected past 30-35 days after the study treatment stop for all AEs that were ongoing at the end of treatment as well as new SAEs (information may be obtained via phone call). The investigator is responsible for the grading of each category mentioned in Section **9.5.1.2**.

…

Section 7.5.4.2: Laboratory examinations

This section was changed as a result of Modification 5.

Old text:

…

Blood tests:

Hematology and biochemistry parameters (for details see Table 16-4)

Serum creatinine concentration will be used to estimate the subject's glomerular filtration rate (eGFR) at screening utilizing the Modification of Diet in Renal Disease (MDRD) equation, see Section **16.9**.

Coagulation parameters only for subjects taking anticoagulants

Virology tests

…

New text:

…

Blood tests:

- Hematology and biochemistry parameters (for details see Table 16-4)

  Serum creatinine concentration will be used to estimate the subject's glomerular filtration rate (eGFR) at screening utilizing the Modification of Diet in Renal Disease (MDRD) equation, see Section **16.9**.
- Coagulation parameters for all subjects
- Virology tests

…

Section 9.1: Data recording

This section was changed as a result of Modification 4.

Old text:

…

- Data recorded during the FGFR expression / FGFR mutation testing period (MTD expansion cohorts only)

  Limited data will be recorded for all subjects in the FGFR expression / FGFR mutation testing period as described below:

  - Subject number
  - Demographic data
  - Cancer classification including primary diagnosis (all comer for study Part 1; sqNSCLC, LAC, BC or SCCHN for Part 2), complete medical / oncological history data and TNM classification
  - Life expectancy
  - ECOG Performance Status
  - Information on existence of an archival tumor biopsy specimen
  - Details on collection of fresh tumor material (if applicable)
  - Adverse event(s)

New text:

- Data recorded during the FGFR expression / FGFR mutation testing period (MTD expansion cohorts only)

  Limited data will be recorded for all subjects in the FGFR expression / FGFR mutation testing period as described below:

  - Subject number
  - Demographic data
  - Cancer classification including primary diagnosis (all comer for study Part 1; sqNSCLC, LAC, BC or SCCHN for Part 2), complete medical / oncological history data and TNM classification
  - Life expectancy
  - ECOG Performance Status
  - Information on existence of an archival tumor biopsy specimen
  - Details on collection of fresh tumor material (if applicable)
  - Adverse event(s) <u>only in case an invasive procedure will be performed to obtain tumor material after informed consent</u>

This section was changed as a result of Modification 3.

Old text:

- Data recorded from "only screened subjects (screening failures)" including pre-screening

For screening failures, all items listed below must be documented within the eCRF:

- Subject number
- Date of birth
- …

New text:

- Data recorded from "only screened subjects (screening failures)" including pre-screening

For screening failures, all items listed below must be documented within the eCRF:

- Subject number
- Date of informed consent
- Date of birth

Section 14.1: Study flow chart - amended

This section was changed as a result of Modification 5.

Old text:

Table 14-1: Study flow chart: Pre-Treatment – Study Part 1 and Part 2 - amended

Measures / actions	**FGFR expression / FGFR mutation testing** Only for subjects recruited for MTD expansion cohorts (Part 1 and Part 2)	**Screening** **Within 28 Days***	**Within 7 Days* before first study drug administration**
Signed informed consent	**X**[A1]	**X**[A2]	
Limited inclusion criteria	**X**		
Inclusion / exclusion criteria		**X**	**X**
Demographic data	**X**[K]	**X**[K]	
Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report	**X**[K]	**X**[K]	
Complete medical / oncological history	**X**[K]	**X**[K]	
TNM classification	**X**[K]	**X**[K]	
Concomitant diseases, NYHA grading		**X**	
Review of baseline toxicities	**(X)**	**X**	**X**
Baseline characteristics (smoking habits / history, alcohol consumption)		**X**	
Previous therapy		**X**	
Concomitant therapy		**X**	**X**
Physical examination		**X**	
Body height			**X**
Body weight / calculation of BMI[B]			**X**
Vital signs[C]			**X**
ECOG performance status	**X**	**X**	
12-lead ECG[D]		**X**	
Echocardiography or MUGA scan			**X**
Obtain pre-treatment biopsy[E]		**X**	

Continued

Table 14-1: Study flow chart: Pre-Treatment – Study Part 1 and Part 2 - amended (Continued)

Measures / actions	FGFR expression / FGFR mutation testing Only for subjects recruited for MTD expansion cohorts (Part 1 and Part 2)	Screening	
		Within 28 Days* before first study drug administration	Within 7 Days* before first study drug administration
Obtain archival tissue sample or fresh tumor material for FGFR expression / FGFR mutation testing	**X**		
Stratification of subjects to be enrolled in MTD expansion cohorts (Part 1 and Part 2)(F)	**X**		
Blood / urine collection for safety lab tests(G)		**X**	**X**
Blood (serum) samples collection for biomarker investigations(H)			**X**
Only females: Urine pregnancy test			**X**
Calculation of eGFR(I)			**X**
Ophthalmological examination at consultant		**X**	
CT / MRI scans		**X**	
Documentation of lesion(s) according to RECIST v1.1			**X**
Adverse events(J)	**(X)**	**X**	**X**

*Pre-study examinations may require hospitalization for 1- 2 days.

(A1) Informed consent for FGFR expression / FGFR mutation testing

(A2) Informed consent for study treatment eligibility can be signed before 28-day screening phase.

(B) BMI (body mass index) is calculated by dividing the subject's weight by the square of his / her height (kg/cm^2).

(C) Vital signs (body temperature, respiration, systolic / diastolic blood pressure, heart rate); for methods of measurement, see Section 9.4.1.1 (Cardiovascular assessment) and Section9.5.3.3 (Vital signs).

(D) At screening, ECG readings (in the supine position) should be performed in triplicate in close sequence and not more than 2 minutes apart.

(E) A pre-treatment biopsy at screening will be obtained from all subjects who agreed on this. The biopsy sample will be sent to laboratory for biomarker evaluation, see Table 16-5, Table 16-6 and Table 16-7

(F) For details, see Table 16-6 and Table 16-7.

Continued

Table 14-1: Study flow chart: Pre-Treatment – Study Part 1 and Part 2 - amended (Continued)

(G) Safety lab tests: Virology tests within 28 days before first study drug administration, all other blood and urine tests within 7 days before first study drug administration, for details see Table 16-4. (H) Biomarker investigations in blood (serum) samples: see Table 16-5 - Table 16-7, and separate document e.g. Laboratory Manual for details.

(I) For calculation of eGFR (estimated glomerular filtration rate), see Section 16.9.

(J) Signs and symptoms that existed prior to signing informed consent should be recorded as medical history findings. Signs and symptoms worsened after the informed consent was signed as well as any sign or symptom that begins after the informed consent was signed (even if prior to start of study medication) should be recorded on an adverse event page of the eCRF using CTCAE v4.03.

(K) Documentation has not to be provided twice for subjects enrolled in the MTD expansion cohorts.

New text:

Table 14-1: Study flow chart: Pre-Treatment – Study Part 1 and Part 2 - amended

Measures / actions	**FGFR expression / FGFR mutation testing** Only for subjects recruited for MTD expansion cohorts (Part 1 and Part 2)	**Screening** **Within 28 Days*** **before first study drug administration**	**Screening** **Within 7 Days*** **before first study drug administration**
Signed informed consent	**X**[A1]	**X**[A2]	
Limited inclusion criteria	**X**		
Inclusion / exclusion criteria		**X**	**X**
Demographic data	**X**[K]	**X**[K]	
Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report	**X**[K]	**X**[K]	
Complete medical / oncological history	**X**[K]	**X**[K]	
TNM classification	**X**[K]	**X**[K]	
Concomitant diseases, NYHA grading		**X**	
Review of baseline toxicities	**(X)**	**X**	**X**
Baseline characteristics (smoking habits / history, alcohol consumption)		**X**	
Previous therapy		**X**	
Concomitant therapy		**X**	**X**
Physical examination		**X**	
Body height			**X**
Body weight / calculation of BMI[B]			**X**
Vital signs[C]			**X**
ECOG performance status	**X**	**X**	
12-lead ECG[D]		**X**	
Echocardiography or MUGA scan			**X**
Obtain pre-treatment biopsy[E]		**X**	
Obtain archival tissue sample or fresh tumor material for FGFR expression / FGFR mutation testing	**X**		

Continued

Table 14-1: Study flow chart: Pre-Treatment – Study Part 1 and Part 2 - amended (Continued)

Measures / actions	**FGFR expression / FGFR mutation testing** Only for subjects recruited for MTD expansion cohorts (Part 1 and Part 2)	**Screening**	
		Within 28 Days*	**Within 7 Days* before first study drug administration**
Stratification of subjects to be enrolled in MTD expansion cohorts (Part 1 and Part 2)(F)	**X**		
Blood / urine collection for safety lab tests(G)		**X**	**X**
Blood (serum) samples collection for biomarker investigations(H)			**X**
Only females: Urine pregnancy test			**X**
Calculation of eGFR(I)			**X**
Ophthalmological examination at consultant		**X**	
CT / MRI scans		**X**	
Documentation of lesion(s) according to RECIST v1.1			**X**
Adverse events(J)	**(X)**	**X**	**X**

*Pre-study examinations may require hospitalization for 1- 2 days.

(A1) Informed consent for FGFR expression / FGFR mutation testing

(A2) Informed consent for study treatment eligibility can be signed before 28-day screening phase.

(B) BMI (body mass index) is calculated by dividing the subject's weight by the square of his / her height (kg/cm^2).

(C) Vital signs (body temperature, respiration, systolic / diastolic blood pressure, heart rate); for methods of measurement, see Section 9.4.1.1 (Cardiovascular assessment) and Section9.5.3.3 (Vital signs).

(D) At screening, ECG readings (in the supine position) should be performed in triplicate in close sequence and not more than 2 minutes apart.

(E) A pre-treatment biopsy at screening will be obtained from all subjects who agreed on this. The biopsy sample will be sent to laboratory for biomarker evaluation, see Table 16-5, Table 16-6 and Table 16-7.

(F) For details, see Table 16-6and Table 16-7.

(G) Safety lab tests: Virology tests within 28 days before first study drug administration, all other blood and urine tests within 7 days before first study drug administration, for details see Table 16-4.

Continued

Table 14-1: Study flow chart: Pre-Treatment – Study Part 1 and Part 2 - amended (Continued)

(H)	Biomarker investigations in blood (serum) samples: see Table 16-5 - Table 16-7, and separate document e.g. Laboratory Manual for details.
(I)	For calculation of eGFR (estimated glomerular filtration rate), see Section 16.9.
(J)	Signs and symptoms that existed prior to signing informed consent should be recorded as medical history findings. Signs and symptoms worsened after the informed consent was signed as well as any sign or symptom that begins after the informed consent was signed (even if prior to start of study medication) should be recorded on an adverse event page of the eCRF using CTCAE v4.03. AE does only to be recorded for period of FGFR expression / FGFR mutation testing in pre-treatment in case an invasive procedure was performed to obtain tumor material.
(K)	Documentation has not to be provided twice for subjects enrolled in the MTD expansion cohorts.

Section 14.2: Laboratory examinations - amended

This section was changed as a result of Modification 5.

Old text:

Table 14-4: Parameters and time points of laboratory examinations performed at local laboratory or study site (safety laboratory) – Study Part 1 and Part 2 – amended

Parameters	PRE-TREATMENT		TREATMENT						FOLLOW-UP	
	FGFR expression / FGFR mutation testing	Screening	Cycle 1	Cycles 2-12			Cycle ≥13		EOT visit	FU visit
			Day -3	Day 1	Day 8	Day 15	Day 1	Day 11		
BLOOD										
Hematology: Erythrocytes (RBC), hemoglobin, hematocrit, platelet count, MCV, MCH, MCHC, leucocytes (WBC), including differential WBC (absolute count of neutrophils, lymphocytes, monocytes, basophils, and eosinophils)		X	X	X	X	X	X	X	X	~~X~~
Coagulation: PT or PT-INR (obligatory at screening) and PTT (aPTT)[(A)]		X	~~X~~	X	~~X~~	~~X~~	X	~~X~~	X	~~X~~
Biochemistry: AST / GOT, ALT / GPT, gamma-GT, AP, LDH, amylase, lipase, glucose, triglycerides, creatinine[(B)], BUN, uric acid, bilirubin (total & direct), total protein, albumin, sodium, potassium, chloride, CPK, calcium, phosphate		X	X	X	X	X	X	X	X	~~X~~
Virology: HBs-Ag, anti-HCV, anti-HIV 1+2		X								
URINE										
Macroanalysis: Clarity of urine: clear, slightly clear, cloudy, or turbid		X	X	X	X	X	X	X	X	~~X~~
Urinalysis (dip stick): pH, blood, protein, glucose, bilirubin, urobilinogen, ketone, nitrite, leucocytes (or leucocyte esterase), specific gravity		X	X	X	X	X	X	X	X	~~X~~
Laboratory analysis[(C)]: Protein and creatinine		X	X	X	X	X	X	X	X	~~X~~
Microscopic urinalysis[(D)]: Erythrocytes, leucocytes, epithelia cells, bacteria crystals, casts, bacteria and yeast		X	X	X	X	X	X	X	X	~~X~~

Continued

Table 14-4: Parameters and time points of laboratory examinations performed at local laboratory or study site (safety laboratory) – Study Part 1 and Part 2 – amended (Continued)

Parameters	PRE-TREATMENT		TREATMENT						FOLLOW-UP	
	FGFR expression / FGFR mutation testing	Screening	Cycle 1	Cycles 2-12			Cycle ≥13		EOT visit	FU visit
			Day -3	Day 1	Day 8	Day 15	Day 1	Day 11		
Pregnancy test(F)		X								

A) ~~Only for subjects taking anticoagulant e.g. warfarin or heparin~~
(B) The serum creatinine concentration is used to estimate the subject's glomerular filtration rate (see Section **16.9**)
(C) Random urine sample preferably taken at mid-morning for the quantification of proteinuria by urinary protein/creatinine ratio
(D) Only if urine appearance is turbid, or if protein, leukocytes, erythrocytes, or nitrite are out of normal range)
(F) Only females of childbearing potential

New text:

Table 14-4: Parameters and time points of laboratory examinations performed at local laboratory or study site (safety laboratory) – Study Part 1 and Part 2 – amended

Parameters	PRE-TREATMENT		TREATMENT						FOLLOW-UP	
	FGFR expression / FGFR mutation testing	Screening	Cycle 1	Cycles 1-12			Cycle ≥13		EOT visit	FU visit
			Day -3	Day 1	Day 8	Day 15	Day 1	Day 11		
BLOOD										
Hematology: Erythrocytes (RBC), hemoglobin, hematocrit, platelet count, MCV, MCH, MCHC, leucocytes (WBC), including differential WBC (absolute count of neutrophils, lymphocytes, monocytes, basophils, and eosinophils)		X	X	X	X	X	X	X	X	
Coagulation: PT or PT-INR (obligatory at screening) and PTT (aPTT)[(A)]		X		X			X		X	
Biochemistry: AST / GOT, ALT / GPT, gamma-GT, AP, LDH, amylase, lipase, glucose, triglycerides, creatinine[(B)], BUN, uric acid, bilirubin (total & direct), total protein, albumin, sodium, potassium, chloride, CPK, calcium, phosphate		X	X	X	X	X	X	X	X	
Virology: HBs-Ag, anti-HCV, anti-HIV 1+2		X								
URINE										
Macroanalysis: Clarity of urine: clear, slightly clear, cloudy, or turbid		X	X	X	X	X	X	X	X	
Urinalysis (dip stick): pH, blood, protein, glucose, bilirubin, urobilinogen, ketone, nitrite, leucocytes (or leucocyte esterase), specific gravity		X	X	X	X	X	X	X	X	
Laboratory analysis[(C)]: Protein and creatinine		X	X	X	X	X	X	X	X	
Microscopic urinalysis[(D)]: Erythrocytes, leucocytes, epithelia cells, bacteria crystals, casts, bacteria and yeast		X	X	X	X	X	X	X	X	
Pregnancy test[(F)]		X								

Continued

Table 14-4: Parameters and time points of laboratory examinations performed at local laboratory or study site (safety laboratory) – Study Part 1 and Part 2 – amended

(A)	For all subjects
(B)	The serum creatinine concentration is used to estimate the subject's glomerular filtration rate (see Section **16.9**)
(C)	Random urine sample preferably taken at mid-morning for the quantification of proteinuria by urinary protein/creatinine ratio
(D)	Only if urine appearance is turbid, or if protein, leukocytes, erythrocytes, or nitrite are out of normal range)
(F)	Only females of childbearing potential

Section 14.2: Laboratory examinations - amended

This section was changed as a result of Modification 6.

Old text:

Table 14-6: Parameters and time points for biomarker investigations in study Part 1 / MTD expansion (all comer) - amended

Parameters	PRE-TREATMENT		TREATMENT									FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	~~Cycle 1~~ ~~Day 1~~	~~Day 3~~	~~Day 8~~	~~Day 15~~	Cycles ~~2~~-12 Day 1	Day 8	Day 15	Cycles ≥13 Day 1	Day 11	EOT visit
Tumor tissue:												
p-ERK1/2 levels		X(A)					X(B) only Cycle 2					
FGFR1/2/3 expression	X(C)											
FGFR and FGFR pathway mutations	X(C)											
Blood (serum) samples*:												
FGF23		X	~~X~~	~~X~~	~~X~~	~~X~~	X	X	X	X	X	X
Phosphate, Calcium		X	~~X~~	~~X~~	~~X~~	~~X~~	X	X	X	X	X	X

p-ERK = phospho-extracellular signal–regulated kinase
FGFR 1/2/3 = fibroblast growth factor receptor 1, 2 and 3
FGF23 = fibroblast growth factor 23

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877 only for Cycle 1.

(A) An additional biopsy is not requested if a biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit. Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

Continued

Table 14-6: Parameters and time points for biomarker investigations in study Part 1 / MTD expansion (all comer) - amended

Parameters	PRE-TREATMENT		TREATMENT							FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	~~Cycle 1~~ ~~Day 1~~	~~Day 3~~	~~Day 8~~	~~Day 15~~	Cycles ~~2~~-12 Day 1	Day 8	Day 15	Cycles ≥13 Day 1	Day 11	EOT visit
(B) A second mandatory tumor biopsy must be obtained on Cycle 2, Day 1.												
(C) An archival or fresh tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels, necessary for subject stratification (see Section 7.1.1: Inclusion criteria). If no archival biopsy sample is available which has been handled and processed as described in the lab manual, collection of fresh tumor biopsy material is mandatory for stratification. The evaluation of FGFR pathway mutations is planned retrospectively for all subjects.												

New text:

Table 14-6: Parameters and time points for biomarker investigations in study Part 1 / MTD expansion (all comer) - amended

Parameters	PRE-TREATMENT		TREATMENT					FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycles 1-12 Day 1	Day 8	Day 15	Cycles ≥13 Day 1	Day 11	EOT visit
Tumor tissue:								
p-ERK1/2 levels		X(A)	X(B) only Cycle 2					
FGFR1/2/3 expression	X(C)							
FGFR and FGFR pathway mutations	X(C)							
Blood (serum) samples*:								
FGF23		X	X	X	X	X	X	X
Phosphate, Calcium		X	X	X	X	X	X	X

p-ERK = phospho-extracellular signal–regulated kinase
FGFR 1/2/3 = fibroblast growth factor receptor 1, 2 and 3
FGF23 = fibroblast growth factor 23

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877 only for Cycle 1.

(A) An additional biopsy is not requested if a biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit. Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

(B) A second mandatory tumor biopsy must be obtained on Cycle 2, Day 1.

Continued

Table 14-6: Parameters and time points for biomarker investigations in study Part 1 / MTD expansion (all comer) - amended

Parameters	PRE-TREATMENT		TREATMENT					FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycles 1-12 Day 1	Cycles 1-12 Day 8	Cycles 1-12 Day 15	Cycles ≥13 Day 1	Cycles ≥13 Day 11	EOT visit
(C) An archival or fresh tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels, necessary for subject stratification (see Section 7.1.1: Inclusion criteria). If no archival biopsy sample is available which has been handled and processed as described in the lab manual, collection of fresh tumor biopsy material is mandatory for stratification. The evaluation of FGFR pathway mutations is planned retrospectively for all subjects.								

Section 14.2: Laboratory examinations - amended

This section was changed as a result of Modification 6. *Old text:*

Table 14-7: Parameters and time points for biomarker investigations in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) - amended

Parameters	PRE-TREATMENT		TREATMENT					FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycles 2-12			Cycles ≥13		EOT visit
			Day 1	Day 8	Day 15	Day 1	Day 11	
Tumor tissue:								
p-ERK1/2 levels		X(A)	X(B) only Cycle 2					
FGFR1/2/3 expression	X(C)							
FGFR and FGFR pathway mutations	X(C)							
Blood (serum) samples*:								
FGF23		X	X	X	X	X	X	X
Phosphate, calcium		X	X	X	X	X	X	X

p-ERK = phospho-extracellular signal–regulated kinase
FGFR 1/2/3 = fibroblast growth factor receptor 1, 2 and 3
FGF23 = fibroblast growth factor 23

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877 only for Cycle 1.

(A) A pre-treatment biopsy (e.g. endoscopic or ultrasound-guided biopsy) will be obtained at screening if the subject agreed on this. The pre-treatment biopsy is optional for subjects for whom an archival biopsy is available. An additional biopsy is not requested if a biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit.
Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

(B) A second biopsy will be taken on Cycle 2, Day 1 if the subject agreed on this at screening (optional biopsy).

Continued

Table 14-7: Parameters and time points for biomarker investigations in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) - amended

(C) An archival tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels necessary for subject stratification (see Section 7.1.1: Inclusion criteria). If no archival biopsy is available which has been handled and processed as described in the lab manual, collection of fresh tumor biopsy material is mandatory for stratification. Samples of BC subjects will also be tested on activating FGFR3 mutation status for stratification. The evaluation of FGFR pathway mutations is planned retrospectively for all subjects.
p-ERK1/2 levels will only be analyzed if a subject is willing to undergo both a pre-treatment biopsy at screening and a second biopsy on Cycle 2, Day 1.

New text:

Table 14–7: Parameters and time points for biomarker investigations in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) - amended

Parameters	PRE-TREATMENT		TREATMENT					FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycles 1-12			Cycles ≥13		EOT visit
			Day 1	Day 8	Day 15	Day 1	Day 11	
Tumor tissue:								
p-ERK1/2 levels		X(A)	X(B) only Cycle 2					
FGFR1/2/3 expression	X(C)							
FGFR and FGFR pathway mutations	X(C)							
Blood (serum) samples*:								
FGF23		X	X	X	X	X	X	X
Phosphate, calcium		X	X	X	X	X	X	X

p-ERK = phospho-extracellular signal–regulated kinase
FGFR 1/2/3 = fibroblast growth factor receptor 1, 2 and 3
FGF23 = fibroblast growth factor 23

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877 only for Cycle 1.

(A) A pre-treatment biopsy (e.g. endoscopic or ultrasound-guided biopsy) will be obtained at screening if the subject agreed on this. The pre-treatment biopsy is optional for subjects for whom an archival biopsy is available. An additional biopsy is not requested if a biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit.
Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

(B) A second biopsy will be taken on Cycle 2, Day 1 if the subject agreed on this at screening (optional biopsy).

Continued

Table 14–7: Parameters and time points for biomarker investigations in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) - amended

(C) An archival tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels necessary for subject stratification (see Section 7.1.1: Inclusion criteria). If no archival biopsy is available which has been handled and processed as described in the lab manual, collection of fresh tumor biopsy material is mandatory for stratification. Samples of BC subjects will also be tested on activating FGFR3 mutation status for stratification. The evaluation of FGFR pathway mutations is planned retrospectively for all subjects.
p-ERK1/2 levels will only be analyzed if a subject is willing to undergo both a pre-treatment biopsy at screening and a second biopsy on Cycle 2, Day 1.

15.5 Amendment 5

Date of amendment: 16 September 2016

15.5.1 Overview of changes

15.5.1.1 Modification 1: Increase in number of patients with BC

Description of modification to the study plan

The number of subjects with BC to be included will be increased to ensure 30 evaluable subjects completed Cycle 2. Selected safety-relevant in- and exclusion criteria will be modified. Moreover, the study will be performed worldwide.

Rationale for introducing the modification

In order to confirm the efficacy and safety signals in patients with relapsed or refractory bladder cancer overexpressing FGFR or with activating FGFR3 mutations the recruitment will be extended to ensure overall treatment of approximately 30 evaluable subjects.. Based on the current available overall safety database which shows good tolerability, some in- and exclusion criteria will be adapted.

List of CSP sections affected by this modification

Synopsis, Sections: 6 Study design, 6.2 Justification of the study design, 7.1.1.2 Eligibility criteria for study treatment, 7.1.2.3 Exclusion criteria, 7.5.4 Echocardiography / MUGA scan, 10.7 Determination of sample size.

15.5.1.2 Modification 2: PK assessment in renally impaired subjects

Description of modification to the study plan

A maximum of 8 subjects with moderate renal impairment (Glomerular filtration rate (GFR) 30-59 mL/min/1.73 m^2) will be included and the PK will be assessed. To allow recruitment of these subjects inclusion criteria are modified.

Rationale for introducing the modification

Assessment of PK in this patient population may allow dosing of BAY 1163877 in patients with moderate renal impairment.

List of CSP sections affected by this modification

Synopsis, Sections: 6 Study design, 9.4.2.1 Drug measurement, 10.7 Determination of sample size, 16.1 Study flow chart

15.5.1.3 Modification 3: ECG recording

Description of modification to the study plan

All ECGs will be recorded as single ECGs.

Rationale for introducing the modification

Triplicate ECGs were collected in patients enrolled under the study protocol versions 1-5.

The established data base is expected to be sufficient to model changes of QT after BAY1163877 dosing, i.e. single ECGs for safety assessment are sufficient.

List of CSP sections affected by this modification

Synopsis, Sections: 6 Study design, 9.1.2.1.2 Screening, 9.1.2.3.1 Cycle 1, 9.5.3.4 Electrocardiogram, 16.1 Study flow chart.

15.5.1.4 Modification 4: Biomarker assessment in serum

Description of modification to the study plan

Assessment of biomarkers in blood will no longer be performed.

Rationale for introducing the modification

A sufficient set of data was collected to correlate BAY1163877 dosing and changes of FGFR23. Serum calcium and phosphate will continue to be monitored in the safety assessments.

List of CSP sections affected by this modification

Synopsis, Sections: 6 Study design, 9.1.2.1.2 Screening, 9.1.2.3.1 Cycle 1, 9.1.2.3.2 Subsequent Cycles (Cycles 2-13), 9.1.2.3.3 Subsequent Cycles (Cycles ≥13), 9.1.2.3.4 Follow up, 9.4.4 Biomarker investigation, 9.5.4.2 Laboratory examinations, 16.1 Study flow chart, 16.2 Laboratory examinations.

15.5.1.5 Modification 5: Dose administration

Description of modification to the study plan

BAY 1163877 can be administered regardless of food intake.

Rationale for introducing the modification

No changes of the PK of BAY 1163877 was observed after intake of food.

List of CSP sections affected by this modification

Sections 8.4.2.2 and 8.4.2.2.1.

15.5.1.6 Modification 6: Minor corrections/inconsistencies/change of sponsor name

Description of modification to the study plan

Minor text modifications and corrections of omissions or terminology were done. Moreover, section numbering was amended according to the current template (i.e. title page and synopsis were numbered at level 1). Therefore, all following section numbers changed accordingly.

Rationale for introducing the modification

These changes were done for clarification and to ensure correct and consistent wording. Moreover, the name of the sponsor Bayer Health Care AG was renamed to Bayer AG. The data management department of Nuvisan became part of Linical.

List of CSP sections affected by this modification

Title page, Synopsis, Sections: 6 Study design, 8.2 Identity of study treatment, 8.9.1 Drug-drug interaction relevant for BAY 1163877, 8.9.2 Prohibited concomitant medication, 8.9.3 Permitted concomitant medication, 9.3.1 Tumor evaluation, 9.4.1.1 Cardiovasvular assessments, 9.5.3.2 Ophthalmological examination, 11.1 Data recording, 11.3 Data processin, 16.8 Response evaluation criteria in solid tumors.

15.5.2 Changes of protocol

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment. Deletions are crossed out in the "old text". Additions are underlined in the "new text". Corrections of typing errors, omissions or terminology (minor corrections) are not highlighted in this amendment.

15.5.2.1 Title page

This section was changed as a result of Modifications 1 and 6.

Old text:

Title page

Bayer HealthCare

Integrated Clinical Study Protocol
No. BAY 1163877 / 16443

Sponsor: **Bayer ~~HealthCare~~ AG, D-51368 Leverkusen, Germany**

New text:

1 Title page

Integrated Clinical Study Protocol
No. BAY 1163877 / 16443

Sponsor:

<u>Sponsor (Non-US): Bayer AG,</u> D-51368 Leverkusen, Germany

<u>Sponsor (US territory): Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA</u>

15.5.2.2 Synopsis

This section was changed as a result of Modifications 1, 2, 3, 4 and 6.

Old text:

Synopsis

Diagnosis and main criteria for inclusion	• ….. • Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting the study treatment: - ~~Hemoglobin ≥ 9.0 g/dL; subjects taking chronic erythropoietin consistent with institutional guidelines can be included~~. - ….. - ~~Amylase and~~ lipase ≤ ~~2.5~~ x ULN - … - Glomerular filtration rate (GFR) ≥ ~~60~~ mL/min/1.73 m^2 according to the modified diet in renal disease (MDRD) abbreviated formula • ….
Methodology	Eligible cancer subjects will be enrolled at multiple centers ~~in Europe and Asia~~. In total, the "on study" period for the subjects comprises 3 phases: … The complete duration of the study (Part 1 and Part 2) depends on the number of dose-escalation steps in Part 1 and will be approximately ~~2~~ years. … **Electrocardiogram (ECG):** 12-lead ECG readings will be performed at screening, on Cycle 1, Days -3 and -2 ("tablet bridging cohort" and "food effect assessment" only), on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle, and at the EOT visit. ~~**At screening and in Cycle 1, ECG readings should be done in triplicate.** The triplicate ECGs will be recorded in close sequence and not more than 2 minutes apart. In all subsequent Cycles (Cycle ≥ 2) and at the EOT visit, ECG readings will be performed as single~~

	~~readings.~~ **Pharmacodynamic (PD) biomarkers:** In an attempt to demonstrate the mechanism of action of BAY 1163877, biomarkers will be studied in ~~blood (serum) and~~ tissue samples. **~~Biomarker analysis in serum~~** ~~Blood (serum) samples for quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected at screening, on Days 1*, 8* and 15* of Cycles 1-12, on Days 1 and 11 of Cycles ≥ 13, and at EOT visit. In subjects included in study Part 1 (all comer) an additional blood (serum) sample will be collected on Cycle 1, Day 3*.~~ ~~* Blood collection before administration of morning dose only for Cycle 1 of Part 1 and Part 2.~~ **Biomarker analysis in tumor tissue** …
Number of subjects	~~Approximately 200~~ subjects will be enrolled in the pre-treatment phase of the study. … • *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)*: ~~40~~ additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and a cohort of ~~20~~ evaluable subjects with BC or SCCHN treated at MTD ~~(at least 8 subjects per indication)~~.

New text:

2 Synopsis

Diagnosis and main criteria for inclusion	• … • Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting the study treatment: - … - Lipase ≤ 5 x ULN - … - Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 according to the modified diet in renal disease (MDRD) abbreviated formula • …
Methodology	Eligible cancer subjects will be enrolled at multiple centers worldwide. In total, the "on study" period for the subjects comprises 3 phases: … The complete duration of the study (Part 1 and Part 2) depends on the number of dose-escalation steps in Part 1 and will be approximately 7 years. … **Pharmacokinetics (PK):** … In the MTD expansion cohorts, in a maximum of 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated formula), serial PK blood samples will be collected on Cycle 1 Day 1 and Day 15. … **Electrocardiogram (ECG):** 12-lead ECG readings will be performed at screening, on Cycle 1, Days -3 and -2 ("tablet bridging cohort" and "food effect assessment" only), on Cycle 1, Days 1, 2, and 15, thereafter on

	Day 1 of each subsequent Cycle, and at the EOT visit. **Pharmacodynamic (PD) biomarkers:** In an attempt to demonstrate the mechanism of action of BAY 1163877, biomarkers will be studied in tissue samples. **Biomarker analysis in tumor tissue** …
Number of subjects	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. …. • *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)*: Additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and a cohort of approximately 30 evaluable subjects with BC and at least 8 subjects with SCCHN treated at MTD.

15.5.2.3 6. Study design

This section was changed as a result of Modifications 1, 2, 3, 4 and 6.

Old text:

Design overview

This is a Phase I, first-in-human, open-label, non-randomized, multi-center, 2-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 ~~in Europe and Asia~~.

…

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

…

~~It is expected that approximately 200~~ subjects will be enrolled in the pre-treatment phase of the study ~~and approximately 92 subjects will be enrolled in~~ the treatment phase.

…

Targeted / planned enrollment:

…

- *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)*: ~~40~~ additional

subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and ~~20~~ evaluable subjects with BC or SCCHN ~~(at least 8 subjects per indication)~~ treated at MTD.

PK assessments will be performed in all subjects participating in study Part 1 / dose escalation and MTD expansion (all comer). 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. 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.

…

Treatment: Subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects of study Part 2) will receive BAY 1163877 (tablet or solution) on a continuous schedule starting with single-dose administration on Cycle 1, Day 1, followed by a "drug-free day" (to enable single dose PK assessments). 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 the maximum tolerated dose is determined.~~

…

Pharmacokinetics (PK): Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 in the "tablet bridging cohort", and on Cycle 1, Days 1 and 15 in all subjects participating in Part 1 (all comer) and in at least 12 subjects participating in Part 2 (sqNSCLC + LAC + BC + SCCHN). In approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2), the effect of food on the PK of BAY 1163877 will be determined by comparing exposures on Cycle 1 Day -3 (administration after consumption of a high-fat, high-calorie breakfast) and Cycle 1 Day 1 (administration after an overnight fast of at least 8 hours), see Section 8.1.

…

Electrocardiogram (ECG): 12-lead ECG readings will be performed at screening, on Cycle 1, Days -3 and -2 ("tablet bridging cohort" and "food effect assessment", only), on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle, and at the EOT visit. ~~**At screening and in Cycle 1, ECG readings should be done in triplicate.** The triplicate ECGs will be recorded in close sequence and not more than 2 minutes apart.~~ In all ~~subsequent~~ Cycles ~~(Cycle ≥ 2)~~ and at the EOT visit, ECG readings will be performed as single readings. The time points for ECG readings and further details are provided in Section 9.5.3.4.

Pharmacodynamic (PD) biomarkers: In an attempt to demonstrate the mechanism of action of BAY 1163877 biomarkers will be studied in ~~blood (serum) and~~ tissue samples (for details see Section 9.4.4).

~~*Biomarker analysis in serum:* Blood (serum) samples for quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected at screening, on~~

~~Days 1, 8 and 15 of Cycles 1-12, on Days 1 and 11 of Cycles ≥13, and at EOT visit. In subjects included in study Part 1 (all comer) an additional blood (serum) sample will be collected on Cycle 1, Day 3.~~ *Biomarker analysis in tumor tissue:* Biomarker analysis will be done at screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN) according to FGFR expression levels / FGFR mutation using either an archival tumor tissue specimen or fresh tumor biopsy material (see Section 7.1.1, inclusion criteria).

New text:

Design overview

This is a Phase I, first-in-human, open-label, non-randomized, multi-center, 2-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.

…

The complete duration of the study (Part 1 and Part 2) 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 in the screening phase of the treatment phase.

…

Targeted / planned enrollment:

…

- *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)*: additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and approximately 30 evaluable subjects with BC and at least 8 subjects with SCCHN treated at MTD.

PK assessments will be performed in all subjects participating in study Part 1 / dose escalation and MTD expansion (all comer). 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 a maximum of 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.

…

Treatment: Subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects of study Part 2 and a maximum of 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 "drug-free day" (to enable single dose PK assessments). 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.

…

Pharmacokinetics (PK): Single- and multiple-dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day -3 in the "tablet bridging cohort", and on Cycle 1, Days 1 and 15 in all subjects participating in Part 1 (all comer) and in at least 12 subjects participating in Part 2 (sqNSCLC + LAC + BC + SCCHN). In approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2), the effect of food on the PK of BAY 1163877 will be determined by comparing exposures on Cycle 1 Day -3 (administration after consumption of a high-fat, high-calorie breakfast) and Cycle 1 Day 1 (administration after an overnight fast of at least 8 hours), see Section 8.1. In the MTD expansion cohorts, in a maximum of 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated formula), serial PK blood samples will be collected on Cycle 1 Day 1 and Day 15.

…

Electrocardiogram (ECG): 12-lead ECG readings will be performed at screening, on Cycle 1, Days -3 and -2 ("tablet bridging cohort" and "food effect assessment", only), on Cycle 1, Days 1, 2, and 15, thereafter on Day 1 of each subsequent Cycle, and at the EOT visit. In all Cycles and at the EOT visit, ECG readings will be performed as single readings. The time points for ECG readings and further details are provided in Section 9.5.3.4.

Pharmacodynamic (PD) biomarkers: In an attempt to demonstrate the mechanism of action of BAY 1163877 biomarkers will be studied in tissue samples (for details see Section 9.4.4).

Biomarker analysis in tumor tissue: Biomarker analysis will be done at screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN) according to FGFR expression levels / FGFR mutation using either an archival tumor tissue specimen or fresh tumor biopsy material (see Section 7.1.1, inclusion criteria).

15.5.2.4 6.2 Justification of the design

This section was changed as a result of Modification 1.

Old text:

The study will be conducted at multiple sites ~~in Europe and Asia~~ to ensure recruitment of a

sufficient number of subjects with advanced solid organ malignancies. The sites must be specialized in tumor assessment according to RECIST 1.1 and must be well equipped to conduct the efficacy and safety evaluations required by the protocol.

…

New text:

The study will be conducted at multiple sites worldwide to ensure recruitment of a sufficient number of subjects with advanced solid organ malignancies. The sites must be specialized in tumor assessment according to RECIST 1.1 and must be well equipped to conduct the efficacy and safety evaluations required by the protocol.

…

15.5.2.5 7.1.1.2 Eligibility criteria for study treatment

This section was changed as a result of Modification 1.

Old text:

…..

- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting the study treatment:

- ~~Hemoglobin ≥ 9.0 g/dL; subjects taking chronic erythropoietin consistent with institutional guidelines can be included.~~

- ~~…..~~

- ~~Amylase and~~ lipase ≤ ~~2.5~~ x ULN

- …

- Glomerular filtration rate (GFR) ≥ ~~60~~ mL/min/1.73 m^2 according to the modified diet in renal disease (MDRD) abbreviated formula

….

New text:

…

- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting the study treatment:

- …

- Lipase ≤ 5 x ULN

- …

- Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 according to the modified diet in renal disease (MDRD) abbreviated formula

…

15.5.2.6 7.1.2.3 Exclusion criteria

This section was changed as a result of Modification 1.

Old text:

…

Medical and surgical history

…

- History or current condition of an uncontrolled cardiovascular disease including congestive heart failure (CHF) > NYHA (New York Heart Association) Class 2, unstable angina (symptoms of angina at rest) or new-onset angina (within last 3 months) or myocardial infarction (MI) within past 6 months and cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted)

- ~~Left ventricular ejection fraction (LVEF) < 50% as assessed by echocardiography performed at screening~~

- ~~Subjects with history and / or current evidence of endocrine alteration of calciumphosphate homeostasis (e.g. parathyroid disorder, history of parathyroidectomy, tumor lysis, tumoral calcinosis)~~

- ~~Prior pancreatitis, intra- or extrahepatic biliary obstruction within the previous 12 months, or history of malignant obstruction requiring biliary stent unless stably treated with no prior obstruction or blockage of stent~~

- ~~Pericarditis~~

- ~~Current evidence of corneal disorder / keratopathy including but not limited to bullous / band keratopathy, corneal abrasion, inflammation / ulceration, keratoconjunctivitis etc. (to be confirmed by ophthalmologic examination).~~ ~~Pre-existing cataract is not an exclusion criterion.~~

- History of human immunodeficiency virus (HIV) infection or chronic hepatitis B or C

…

Medication, drug use and special behavioral patterns

- …

- Concomitant therapies that cannot be discontinued or switched to a different medication prior to study entry that are known to increase serum ~~calcium and / or~~ phosphate levels~~, especially calcium, phosphate, vitamin D, parathyroid hormone (parathormone)~~ are not permitted within 4 weeks prior to start of study treatment). ~~Bisphosphonates, zolendronic acid or monoclonal anti-RANK ligand antibodies (denosumab) are allowed.~~

- Anticancer chemotherapy or immunotherapy during the study or within 5-half-lives prior to start of study treatment. Mitomycin C, nitrosoureas or monoclonal antibodies

with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies. Acute toxic effects of previous anticancer chemotherapy or immunotherapy have to be normalized completely (excluding alopecia). Anticancer therapy is defined as any agent or combination of agents with clinically proven anti-tumor activity administered by any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints.

…

Electrocardiogram (ECG), blood pressure, heart rate

- Systolic / diastolic blood pressure ≤ ~~110/70~~ mmHg and heart rate ≥ 100/min (measured with the subject in a sitting position for at least 2 minutes). ~~Measurements will be in duplicate and the mean value will be used for assessment.~~

New text:

…

Medical and surgical history

…

- History or current condition of an uncontrolled cardiovascular disease including congestive heart failure (CHF) > NYHA (New York Heart Association) Class 2, unstable angina (symptoms of angina at rest) or new-onset angina (within last 3 months) or myocardial infarction (MI) within past 6 months and cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted)

- History of human immunodeficiency virus (HIV) infection or chronic hepatitis B or C

…

Medication, drug use and special behavioral patterns

- …

- Concomitant therapies that cannot be discontinued or switched to a different medication prior to study entry that are known to increase serum phosphate levels are not permitted within 4 weeks prior to start of study treatment).

- Anticancer chemotherapy or immunotherapy during the study or within 5-half-lives prior to start of study treatment. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks <u>before starting to receive study treatment or within 6 weeks</u> of pre-treatment biopsy for biomarker (p-ERK1/2) studies. Acute toxic effects of previous anticancer chemotherapy or immunotherapy have to be normalized completely (excluding alopecia). Anticancer therapy is defined as any agent or combination of agents with clinically proven anti-tumor activity administered by any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints.

…

Electrocardiogram (ECG), blood pressure, heart rate

- Systolic / diastolic blood pressure ≤ 100/60 mmHg and heart rate ≥ 100/min (measured with the subject in a sitting position for at least 2 minutes).

15.5.2.7 8.2 Identity of study treatment

This section was changed as a result of Modification 6.

Old text:

Table 6-2: Identity of test drug (IMP): BAY 1163877 tablet formulation

Generic name / brand name / INN	Not applicable
Substance code number(s)	BAY 1163877 as BAY 1213802
Material / formulation) ~~number(s)~~	**~~81820457 for~~** BAY 1163877 HCL TAB 50.0 mg 363 COAT **~~81820449 for~~** BAY 1163877 HCL TAB 200.0 mg 364 COAT

New text:

Table 8-2: Identity of test drug (IMP): BAY 1163877 tablet formulation

Generic name / brand name / INN	Not applicable
Substance code number(s)	BAY 1163877 as BAY 1213802
Material / (formulation)	BAY 1163877 HCL TAB 50.0 mg 363 COAT BAY 1163877 HCL TAB 200.0 mg 364 COAT

15.5.2.8 8.4.2.2 Mode of administration

This section was changed as a result of Modification 5.

Old text:

BAY 1163877 will be administered per os (p.o.) ~~at least 1 hour before or 2 hours after a meal or snack~~. …

New text:

BAY 1163877 will be administered per os (p.o.). …

15.5.2.9 8.4.2.2.1 Food effect assessment

This section was changed as a result of Modification 5.

Old text:

…

Starting with Cycle 1, Day 3, BAY 1163877 will be taken twice daily ~~(at least 1 hour before or 2 hours after a meal)~~.

New text:

…

Starting with Cycle 1, Day 3, BAY 1163877 will be taken twice daily.

15.5.2.10 8.9.1 Drug-drug interactions relevant for BAY 1163877

This section was changed as a result of Modification 6.

Old text:

…

Initial in vitro study results ~~indicate that~~ BAY 1163877 ~~is a~~ mechanism-based (irreversible) ~~inhibitor of~~ CYP 3A4 ~~and additional studies are planned to further investigate~~. Since several commonly used drugs are metabolized by CYP 3A4, subjects should be proactively closely monitored.

…

New text:

…

Initial *in vitro* study results with BAY 1163877 indicate minor mechanism-based (irreversible) inhibition potential towards CYP 3A4. Since several commonly used drugs are metabolized by CYP 3A4, subjects should be proactively closely monitored for side effects of these comedications due to potentially increased systemic exposure.

…

15.5.2.11 8.9.2 Prohibited concomitant therapy

This section was changed as a result of Modification 6.

Old text:

Concomitant therapy with the following medication is NOT allowed:

- Anticancer chemotherapy or immunotherapy during the study or within 5-half-lives prior to start of study treatment. Acute toxic effects of previous anticancer chemotherapy or immunotherapy have to be normalized completely (excluding alopecia, anemia and / or hypothyroidism). Anticancer therapy is defined as any agent or combination of agents with clinically proven anti-tumor activity administered by any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints.

…

New text:

Concomitant therapy with the following medication is NOT allowed:

- Anticancer chemotherapy or immunotherapy during the study or within 5-half-lives prior to start of study treatment. Antibody treatment should not be given within 6 weeks before starting to receive study treatment. Acute toxic effects of previous anticancer chemotherapy or immunotherapy have to be normalized completely (excluding alopecia, anemia and / or hypothyroidism). Anticancer therapy is defined as any agent or

combination of agents with clinically proven anti-tumor activity administered by any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints.

…

15.5.2.12 8.9.3 Permitted concomitant therapy

This section was changed as a result of Modification 6.

Old text:

…

- Antiemetic therapy with 5-hydroxytryptamine-3-receptor antagonist and dexamethasone is allowed.

…

New text:

…

- Antiemetic therapy is allowed.

…

15.5.2.13 9.1.2.1.2 Screening

This section was changed as a result of Modifications 3, 4 and 6.

Old text:

….

Within 28 Days Prior to First Dose of BAY 1163877

…

- ~~Triplicate~~ 12-lead ECG readings (see Section 9.5.3.4)

…

Within 7 Days Prior to First Dose of BAY 1163877

…

- ~~Echocardiography or MUGA scan~~
- Blood and urine collection for safety laboratory tests, for details see Table 16-4
- ~~Blood (serum) samples collection for biomarker investigations, see Section 14.2~~

…

New text:

…

Within 28 Days Prior to First Dose of BAY 1163877

…

- Single 12-lead ECG reading (see Section 9.5.3.4)

…

Within 7 Days Prior to First Dose of BAY 1163877

…

- Blood and urine collection for safety laboratory tests. In case of abnormal results caused by intercurrent diseases, short-term treatable conditions or other temporary health disorders, the investigator may decide to repeat the respective screening parameter(s). As a rule, up to 2 repetitions are acceptable, for details see Table 16-4

…

15.5.2.14 9.1.2.3.1 Cycle 1

This section was changed as a result of Modifications 3 and 4.

Old text:

…

Days 1-3 (possible overnight stay)

Day 1

…

- ~~Triplicate~~ 12-lead ECG readings~~s~~ (see Section 9.5.3.4)

…

- ~~Blood (serum) samples collection for biomarker investigations, see Section 14.2~~
- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2)

…

Day 2

- **No administration of BAY 1163877 ("drug-free day") for subjects with PK assessment** (all subjects of study Part 1 and at least 12 subjects with PK assessment in study Part 2 [including "food effect assessment"])

…

- ~~Triplicate~~ ECG readings (see Section 7.5.3.4)

…

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2)

…

Day 3

…

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2)

…

Day 8 ± 1 (Visit)

…

- ~~Blood (serum) samples collection for biomarker investigations, see Section 14.2.~~

…

Day 15

…

- ~~Triplicate~~ ECG readings~~~~ (see Section 7.5.3.4)

…

- ~~Blood (serum) samples collection for biomarker investigations, see Section 14.2.~~
- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2)

…

New text:

…

Days 1-3 (possible overnight stay)

Day 1

…

- Single 12-lead ECG reading (see Section 9.5.3.4)
- …
- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2) and a maximum of 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)

…

Day 2

- **No administration of BAY 1163877 ("drug-free day") for subjects with PK assessment** (all subjects of study Part 1 and at least 12 subjects with PK assessment in study Part 2 and a maximum of 8 subjects with PK assessment in the MTD expansion cohorts with impaired renal function at baseline [including "food effect assessment"])

…

- Single 12-lead ECG readings (see Section 9.5.3.4)

…

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and a maximum of 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)

…

Day 3

…

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and a maximum of 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)

…

Day 15

…

- ECG reading (see Section 7.5.3.4)

…

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and a maximum of 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)

…

15.5.2.15 9.1.2.3.2 Subsequent Cycles (Cycles 2-12)

This section was changed as a result of Modification 4.

Deleted old text:

Day 1 (Visit)

…

- ~~Blood (serum) samples collection for biomarker investigations, see Section 14.2.~~

…

Day 8 ± 1 and Day 15 ± 1 (Visits)

…

- ~~Blood (serum) samples collection for biomarker investigations, see Section 14.2.~~

…

15.5.2.16 9.1.2.3.3 Subsequent Cycles (Cycles ≥13)

This section was changed as a result of Modification 4.

Deleted old text:

Day 1 (Visit)

…

- ~~Blood (serum) samples collection for biomarker investigations, see Section 14.2.~~

…

Day 11 (Visit)

…

- ~~Blood (serum) samples collection for biomarker investigations, see Section 14.2.~~

…

15.5.2.17 9.1.2.3.4 Follow up

This section was changed as a result of Modification 4.

Deleted old text:

…

Within 0-14 Days of Last Study Drug Administration (EOT Visit)

…

- ~~Blood (serum) samples collection for biomarker investigations, see Section 14.2.~~

…

15.5.2.18 9.3.1 Tumor evaluation - response assessment (RECIST)

This section was changed as a result of Modification 6.

Old text:

…

All scans should be done with the identical modality (CT or MRI) and the identical technique (e.g., slice thickness, field of view) to those obtained at baseline. For a response to be scored as complete response (CR) or partial response (PR), the response must be confirmed by a repeat CT scan (with contrast) or MRI scan (with and without contrast) performed ~~8~~ weeks after the response was first determined.

New text:

…

All scans should be done with the identical modality (CT or MRI) and the identical technique (e.g., slice thickness, field of view) to those obtained at baseline. For a response to be scored as complete response (CR) or partial response (PR), the response must be confirmed by a repeat CT scan (with contrast) or MRI scan (with and without contrast) performed not earlier than 4 weeks after the response was first determined.

15.5.2.19 9.4.1.1 Cardiovascular assessment

This section was changed as a result of Modification 6.

Old text:

…

- At screening, BP must be measured in both arms to see whether there is a difference in blood pressure readings between the subject's right and left arm. If one arm has higher blood pressure than the other, that arm should be used for further BP measurements (all further BP measurements must be done on the same arm)
- ~~Measurements (on the same arm) will be in duplicate and the mean value will be used for assessment. If the first two readings differ by more than 5 mmHg, additional readings should be obtained and averaged.~~

New text:

…

- At screening, BP must be measured in both arms to see whether there is a difference in blood pressure readings between the subject's right and left arm. If one arm has higher blood pressure than the other, that arm should be used for further BP measurements (all further BP measurements must be done on the same arm)

…

15.5.2.20 9.4.2.1 Drug measurements

This section was changed as a result of Modification 2.

Old text:

…

Pharmacokinetic assessments will be performed in all subjects enrolled in Part 1 (dose escalation and MTD expansion (all comer) cohorts). The plan is to perform pharmacokinetic assessments in at least 12 subjects in Part 2 MTD expansion cohort (sqNSCLC + LAC + BC + SCCHN) such that valid PK data are available in 8 subjects. "Food effect assessment" will be performed in approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2).

Blood (plasma) samples for PK assessment of BAY 1163877 will be collected at the following time points:

…

- Cycles 2-5, Day 1: exposure-response modelling

…

New text:

…

Pharmacokinetic assessments will be performed in all subjects enrolled in Part 1 (dose

escalation and MTD expansion (all comer) cohorts). The plan is to perform pharmacokinetic assessments in at least 12 subjects in Part 2 MTD expansion cohort (sqNSCLC + LAC + BC + SCCHN) such that valid PK data are available in 8 subjects. "Food effect assessment" will be performed in approximately 8 subjects enrolled in the MTD expansion cohorts (study Part 1 and Part 2). In the MTD expansion cohorts pharmacokinetic assessments will be performed in a maximum of 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated formula).

Blood (plasma) samples for PK assessment of BAY 1163877 will be collected at the following time points:

…

- Cycles 2-5, Day 1: exposure-response modelling (not in subjects with impaired renal function)

…

15.5.2.21 9.4.4 Biomarker investigations

This section was changed as a result of Modification 4 and 6.

Old text:

Concentrations of FGF23 will be measured by a validated ELISA assay. Instructions for sample collection, processing, storage and shipment will be described in a separate document (e.g. lab manual). ~~PD marker investigations~~

Pharmacodynamic (PD) biomarkers:

In an attempt to demonstrate the mechanism of action of BAY 1163877, biomarkers will be studied in ~~blood (serum) and~~ tissue samples.

~~Biomarker analysis in~~ ~~blood (serum) samples~~

~~Blood (serum) samples for the quantification of fibroblast growth factor 23 (FGF23), phosphate and calcium levels will be collected as follows:~~

- ~~Study Part 1 / dose escalation~~
  - ~~Screening~~
  - ~~Cycle 1: Days 1*, 3*, 8*, and 15*~~
  - ~~Cycles 2-12: Days 1, 8, 15~~
  - ~~Cycles ≥13: Days 1 and 11~~
  - ~~EOT visit~~
- ~~Study Part 1 / MTD expansion (all comer) and Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)~~
  - ~~Screening~~

~~- Cycles 1-12: Days 1*, 8*, 15*~~

~~- Cycles ≥13: Days 1 and 11~~

~~- EOT visit~~

~~*Blood collection before administration of morning dose only for Cycle 1 of Part 1 and Part 2.~~

…

New text:

Concentrations of FGF23 will be measured by a validated ELISA assay. Instructions for sample collection, processing, storage and shipment will be described in a separate document (e.g. lab manual).

Pharmacodynamic (PD) biomarkers:

In an attempt to demonstrate the mechanism of action of BAY 1163877, biomarkers will be studied in tissue samples.

…

15.5.2.22 9.5.3.2 Ophthalmological examination

This section was changed as a result of Modification 6.

Old text:

… The ophthalmologist will describe examination findings on an examination worksheet provided by the investigational site. The worksheet will be transferred to the site ~~where the data will be transcribed to the eCRF~~.

New text:

… The ophthalmologist will describe examination findings on an examination worksheet provided by the investigational site. Any findings qualifying as an adverse event will be recorded accordingly.

15.5.2.23 9.5.3.4 Electrocardiogram (ECG)

This section was changed as a result of Modification 3.

Old text:

For the assessment of possible drug effects on QT/ QTc interval duration at pre-defined time points at screening and in Cycle 1, standard 12-lead ECGs will be recorded in triplicates in selected subjects dosed with 50 mg and higher. The triplicate ECGs will be recorded in close sequence and **not more than 2 minutes apart**.

Subjects will have a single ECG recording in all subsequent cycles.

12-lead ECG readings will be performed in the supine position at the following time points:

- Screening (~~triplicate~~ ECG readings)

- Cycle 1, Day -3 and Day -2 (triplicate ECG readings ["tablet bridging cohort" and "food effect assessment" only])
  - before and 2, 3 (Day -3) and 24 (Day -2) hours after single-dose administration
- Cycle 1, Day 1 and Day 2 (~~triplicate~~ ECG readings)
  - before and 2, 3 (Day 1) and 24 (Day 2) hours after single-dose administration
- Cycle 1, Day 15 (~~triplicate~~ ECG readings)
  - before morning dose, and 2 and 3 hours thereafter

…

New text:

For the assessment of possible drug effects on QT/ QTc interval duration at pre-defined time points at screening and in Cycle 1, standard 12-lead ECGs will be recorded in triplicates in selected subjects dosed with 50 mg and higher until implementation of Amendment 5. The triplicate ECGs will be recorded in close sequence and **not more than 2 minutes apart**.

Subjects will have a single ECG recording in all subsequent cycles.

12-lead ECG readings will be performed in the supine position at the following time points:

- Screening (single ECG reading)
- Cycle 1, Day -3 and Day -2 (triplicate ECG readings ["tablet bridging cohort" and "food effect assessment" only])
  - before and 2, 3 (Day -3) and 24 (Day -2) hours after single-dose administration
- Cycle 1, Day 1 and Day 2 (single ECG reading)
  - before and 2, 3 (Day 1) and 24 (Day 2) hours after single-dose administration
- Cycle 1, Day 15 (single ECG reading)

…

15.5.2.24 9.5.4 Echocardiography / MUGA scan

This section was changed as a result of Modification 1.

Old text:

An echocardiography or MUGA (multiple gated acquisition) scan is to be done at screening (within 7 days prior to first study drug administration) to ensure that only subjects with adequate cardiac function (LVEF ≥ 50%) participate in this study.

New text:

An echocardiography or MUGA (multiple gated acquisition) scan is to be done at

screening (within 7 days prior to first study drug administration) to ensure that only subjects with adequate cardiac function (LVEF ≥ 50%) participate in this study. This is no longer needed after implementation of Amendment 5.

15.5.2.25 9.5.3.6 Laboratory examinations

This section was changed as a result of Modification 4.

Deleted old text:

…

The following laboratory analyses will be performed by analysis laboratories:

~~Blood tests:~~

- ~~Blood (serum) samples for quantification of FGF23 levels will be collected prior to administration of study drug and during the study as shown in Section 16.2 in an attempt to demonstrate the mechanism of action of BAY 1163877.~~

…

15.5.2.26 10.7 Determination of sample size

This section was changed as a result of Modifications 1 and 2.

Old text:

…

In study Part 2 / MTD expansion, additional subjects will be included in order to obtain further safety and PK data at the MTD level in ~~at least 40~~ subjects with sqNSCLC, LAC, BC and SCCHN.

New text:

…

In study Part 2 / MTD expansion, additional subjects will be included in order to obtain further safety and PK data at the MTD level in at least 20 subjects with sqNSCLC or LAC, approximately 30 subjects with BC and at least 8 subjects with SCCHN.

15.5.2.27 11.1 Data recording

This section was changed as a result of Modification 6.

Old text:

…

A CRO (~~Nuvisan~~) provides the investigational site with access to an internet / web-based electronic data capture (EDC) computer system (termed "Inform"). Oracle has developed this system as a secured data entry tool that cannot be modified by investigative sites. The customized application for this protocol was developed by ~~Nuvisan~~ and validated according to ~~Nuvisan~~ "Standard Operating Procedures". Edit checks and data logic checks are done at the point of entry and are validated by ~~Nuvisan~~. All data entered into

the system is transferred to a secure server maintained by ~~Nuvisan~~.

Access to the Inform EDC system at the site, at ~~Nuvisan~~ and at Bayer is password protected. Study access is granted to site personnel only after they have been trained in the use of the Inform EDC System by ~~Nuvisan~~ personnel or after a web-based training, either at the investigational site or at the investigators' meeting. ~~Nuvisan~~ and Bayer personnel are also required to complete the training program before they are allowed to access the system. All Inform EDC system training history is documented and maintained by ~~Nuvisan~~.

The Inform EDC System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, and the date and time it was made. This information is available both at the investigator's site and at ~~Nuvisan~~.

…

New text:

A CRO (Linical, formerly part of Nuvisan) provides the investigational site with access to an internet / web-based electronic data capture (EDC) computer system (termed "Inform"). Oracle has developed this system as a secured data entry tool that cannot be modified by investigative sites. The customized application for this protocol was developed by Linical and validated according to Lincical "Standard Operating Procedures". Edit checks and data logic checks are done at the point of entry and are validated by Linical. All data entered into the system is transferred to a secure server maintained by Linical.

Access to the Inform EDC system at the site, at Linical and at Bayer is password protected. Study access is granted to site personnel only after they have been trained in the use of the Inform EDC System by Linical personnel or after a web-based training, either at the investigational site or at the investigators' meeting. Linical and Bayer personnel are also required to complete the training program before they are allowed to access the system. All Inform EDC system training history is documented and maintained by Linical.

The Inform EDC System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, and the date and time it was made. This information is available both at the investigator's site and at Linical.

…

15.5.2.28 11.3 Data processing

This section was changed as a result of Modification 6.

Old text:

…

For data coding (e.g. AEs, medication), ~~Nuvisan~~ will transfer the verbatim terms and internationally recognized and accepted dictionaries will be used by the sponsor.

…

New text:

…

For data coding (e.g. AEs, medication), Linical will transfer the verbatim terms and internationally recognized and accepted dictionaries will be used by the sponsor.

…

15.5.2.29 16.1 Study flow chart

This section was changed as a result of Modifications 2, 3 and 4.

Old text:

Table 14-1: Study flow chart: Pre-Treatment – Study Part 1 and Part 2

Measures / actions	**FGFR expression / FGFR mutation testing** Only for subjects recruited for MTD expansion cohorts (Part 1 and Part 2)	**Screening** **Within 28 Days***	**Within 7 Days* before first study drug administration**
…			
Demographic data	**X(~~K~~)**	**X(~~K~~)**	
Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report	**X(~~K~~)**	**X(~~K~~)**	
Complete medical / oncological history	**X(~~K~~)**	**X(~~K~~)**	
TNM classification	**X(~~K~~)**	**X(~~K~~)**	
…			
~~Echocardiography or MUGA scan~~			**X**
…			
Blood / urine collection for safety lab tests(G)		**X**	**X**
~~Blood (serum) samples collection for biomarker investigations(H)~~			**~~X~~**
Only females: Urine pregnancy test			**X**
Calculation of eGFR(~~I~~)			**X**
Ophthalmological examination at consultant		**X**	
CT / MRI scans		**X**	
Documentation of lesion(s) according to RECIST v1.1			**X**
Adverse events(~~J~~)	**(X)**	**X**	**X**

~~(H) Biomarker investigations in blood (serum) samples: see Table 16-5 - Table 16-7, and separate document e.g. Laboratory Manual for details.~~

(~~I~~) For calculation of eGFR (estimated glomerular filtration rate), see Section 14.9.

(~~J~~) Signs and symptoms that existed prior to signing informed consent should be recorded as medical history findings. Signs and symptoms worsened after the informed consent was signed as well as any sign or symptom that begins after the informed consent was signed (even if prior to start of study medication) should be recorded on an adverse event page of the eCRF using CTCAE v4.03. AE does only to be recorded for period of FGFR expression /

FGFR mutation testing in pre-treatment in case an invasive procedure was performed to obtain tumor material.

(~~K~~) Documentation has not to be provided twice for subjects enrolled in the MTD expansion cohorts.

New text:

Table 16-1: Study flow chart: Pre-Treatment – Study Part 1 and Part 2

Measures / actions	**FGFR expression / FGFR mutation testing** Only for subjects recruited for MTD expansion cohorts (Part 1 and Part 2)	**Screening** **Within 28 Days*** **before first study drug administration**	**Within 7 Days***
…			
Demographic data	**X**(J)	**X**(J)	
Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report	**X**(J)	**X**(J)	
Complete medical / oncological history	**X**(J)	**X**(J)	
TNM classification	**X**(J)	**X**(J)	
…			
Blood / urine collection for safety lab tests(G)		**X**	**X**
…			

(H) For calculation of eGFR (estimated glomerular filtration rate), see Section 16.9.

(I) Signs and symptoms that existed prior to signing informed consent should be recorded as medical history findings. Signs and symptoms worsened after the informed consent was signed as well as any sign or symptom that begins after the informed consent was signed (even if prior to start of study medication) should be recorded on an adverse event page of the eCRF using CTCAE v4.03. AE does only to be recorded for period of FGFR expression / FGFR mutation testing in pre-treatment in case an invasive procedure was performed to obtain tumor material.

(J) Documentation has not to be provided twice for subjects enrolled in the MTD expansion cohorts.

Old text:

Table 14-3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1 and Part 2 (continued)

Measures / actions	TREATMENT											FOLLOW-UP
	Cycle 1 (21 days)					Cycles 2-12 (21 days)			Cycles ≥13 (21 days)		EOT Visit Within 0-14 days after last dose	FU-Visit / Phone Call[A] At 30-35 days after last dose
Day (D)	D1	D2	D3	D8 ±1	D15	D1	D8 ±1	D15 ±1	D1	D1 1		
…												
12-lead ECG readings[D]	X	X			X	X			X		X	
…												
~~Blood (serum) samples collection for biomarker investigations[G]~~	~~X~~		~~(X)~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
24-hour urine collection[N]	X											
Obtain tumor biopsy for biomarker tests[H]						X (Cy 2 only)						
PK blood sampling[I]	X→ →X				X							
PK blood sampling for PK / PD modeling[J]						X						
…												
Dispense / return of BAY 1163877 and diary[K]	X		X	X	X	X	X	X	X	X	X	

Table 14-3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1 and Part 2 (Continued)

Administration of BAY 1163877 if PK assessment (~~L~~)	**X**		**Continuous, twice-daily administration**		
Administration of BAY 1163877 if no PK assessment(~~M~~)	**Continuous, twice-daily administration**				

..

(D) In Cycle 1, all 12-lead ECGs should be performed ~~in triplicate in close sequence and **not more than 2 minutes apart**. ECG readings will be performed~~ at the following time points:
Cycle 1, Day 1 and Day 2 (~~triplicate~~ ECG readings~~s~~): before and 2, 3 (Day 1) and 24 (Day 2) hours after single-dose administration
Cycle 1, Day 15 (~~triplicate~~ ECG readings~~s~~): before morning dose, and 2 and 3 hours thereafter
Cycle ≥ 2, Day 1 (single ECG reading): after morning dose
EOT visit (single ECG reading)

(E) Safety laboratory tests, see Table 14-4

(F) For calculation of eGFR (estimated glomerular filtration rate), see Section 14.9

~~(G) Biomarker investigations blood (serum) samples, see Table 14-5 - Table 14-7, and Laboratory Manual for details.~~

(~~H~~) A tumor biopsy on Cycle 2, Day 1 will be obtained from all subjects who agreed on this at screening. The biopsy sample will be send to laboratory for biomarker evaluation, see Table 14–5, Table 14 6and Table 14 7.
A biopsy on Cycle 2, Day 1 is optional …
…for subjects in study Part 1 / dose-escalation (all comer).
…for subjects in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN).
A biopsy on Cycle 2, Day 1 is mandatory …
…for subjects in study Part 1 / MTD expansion (all comer).

(~~I~~) PK sampling will be done as follows (for details see Laboratory Manual):•

- Cycle 1, Day 1: single-dose PK (all subjects of study Part 1 and at least 12 subjects of study Part 2)
  – pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hour(s) after single-dose administration (48-hours sample before morning dose on Day 3)
- Cycle 1, Day 15: multiple-dose PK (all subjects of study Part 1 and at least 12 subjects of study Part 2)
  before and 0.5, 1, 2, 3, 4, 6, 8 and 12 hour(s) after morning dose on Cycle 1, Day 15 (12-hour sample before administration of evening dose)

(~~J~~) All subjects participating in the MTD expansion cohorts (Part 1 or Part 2) 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). The dose needs to be taken under supervision and the time recorded….

(~~K~~) First oral administration of BAY 1163877 on Cycle 1 Day 1 will be done with a member of the site. To have complete control over the distribution and use of the study medication, the drug accountability must be performed before new medication is handed out to the subject. Return of BAY 1163877and diary at EOT visit.

(~~L~~) Subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects of study Part 2) will receive a single-dose of BAY 1163877 on Cycle 1, Day 1 (morning), followed by a "drug-free day" (to enable single dose PK assessments). Subjects with "food effect assessment" in Part 1 and Part 2 take the morning dose after an overnight fast of at least 8 hours (see Section 8.4.2.2.1)….

(~~M~~) Subjects without PK assessment in study Part 2 will receive BAY 1163877 twice daily from Cycle 1, Day 1 ongoing.
(~~N~~) In approximately 8 subjects enrolled in MTD expansion cohorts (study Part 1 and Part 2), urine will be collected for 24 hours after dosing.

New text:

Table 16-3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1 and Part 2 (continued)

Measures / actions	**TREATMENT**											**FOLLOW-UP**
	Cycle 1 (21 days)					**Cycles 2-12 (21 days)**			**Cycles ≥13 (21 days)**		**EOT Visit Within 0-14 days after last dose**	**FU-Visit / Phone Call(A) At 30-35 days after last dose**
Day (D)	D1	D2	D3	D8 ±1	D15	D1	D8 ±1	D15 ±1	D1	D1 1		
…												
12-lead ECG readings(D)	**X**	**X**			**X**	**X**			**X**		**X**	
…												
24-hour urine collection(M)	**X**											
Obtain tumor biopsy for biomarker tests(G)						**X** (Cy 2 only)						
PK blood sampling(H)	**X→ → X**				**X**							

PK blood sampling for PK / PD modeling(I)						X						
…												
Dispense / return of BAY 1163877 and diary(J)	X		X	X	X	X	X	X	X	X	X	
Administration of BAY 1163877 if PK assessment (M)	X		**Continuous, twice-daily administration**									
Administration of BAY 1163877 if no PK assessment(M)	**Continuous, twice-daily administration**											

…

(D) In Cycle 1, all 12-lead ECGs should be performed at the following time points:
Cycle 1, Day 1 and Day 2 (single ECG reading): before and 2, 3 (Day 1) and 24 (Day 2) hours after single-dose administration
Cycle 1, Day 15 (single ECG reading): before morning dose, and 2 and 3 hours thereafter
Cycle ≥ 2, Day 1 (single ECG reading): after morning dose
EOT visit (single ECG reading)

(E) Safety laboratory tests, see Table 16-4

(F) For calculation of eGFR (estimated glomerular filtration rate), see Section 16.9

(G) A tumor biopsy on Cycle 2, Day 1 will be obtained from all subjects who agreed on this at screening. The biopsy sample will be send to laboratory for biomarker evaluation, see Table 14–5, Table 14 6and Table 14 7.
A biopsy on Cycle 2, Day 1 is optional …
…for subjects in study Part 1 / dose-escalation (all comer).
…for subjects in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN).
A biopsy on Cycle 2, Day 1 is mandatory …
…for subjects in study Part 1 / MTD expansion (all comer).

(H) PK sampling will be done as follows (for details see Laboratory Manual):•

- Cycle 1, Day 1: single-dose PK (all subjects of study Part 1 and at least 12 subjects of study Part 2 and a maximum of 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)
  - pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hour(s) after single-dose administration (48-hours sample before morning dose on Day 3)
- Cycle 1, Day 15: multiple-dose PK (all subjects of study Part 1 and at least 12 subjects of study Part 2 and a maximum of 8 subjects of the

MTD expansion cohorts with impaired renal function at baseline)

before and 0.5, 1, 2, 3, 4, 6, 8 and 12 hour(s) after morning dose on Cycle 1, Day 15 (12-hour sample before administration of evening dose)

(I) All subjects participating in the MTD expansion cohorts (Part 1 or Part 2) 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). The dose needs to be taken under supervision and the time recorded.…

(J) First oral administration of BAY 1163877 on Cycle 1 Day 1 will be done with a member of the site. To have complete control over the distribution and use of the study medication, the drug accountability must be performed before new medication is handed out to the subject. Return of BAY 1163877and diary at EOT visit.

(K) Subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects of study Part 2 and a maximum of 8 subjects of the MTD expansion cohorts with impaired renal function at baseline) will receive a single-dose of BAY 1163877 on Cycle 1, Day 1 (morning), followed by a “drug-free day” (to enable single dose PK assessments). Subjects with “food effect assessment” in Part 1 and Part 2 take the morning dose after an overnight fast of at least 8 hours (see Section 8.4.2.2.1)….

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

(M) In approximately 8 subjects enrolled in MTD expansion cohorts (study Part 1 and Part 2), urine will be collected for 24 hours after dosing.

15.5.2.30 16.2 Laboratory examinations

This section was changed as a result of Modification 4.

Old text:

Table 14-7: Parameters and time points for biomarker investigations in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)

Parameters	PRE-TREATMENT		TREATMENT					FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycles 1-12 Day 1	Day 8	Day 15	Cycles ≥13 Day 1	Day 11	EOT visit
Tumor tissue:								
p-ERK1/2 levels		X[(A)]	X[(B)] only Cycle 2					
FGFR1/2/3 expression	X[(C)]							
FGFR and FGFR pathway mutations	X[(C)]							
~~**Blood (serum) samples*:**~~								
~~FGF23~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~Phosphate, calcium~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~

p-ERK = phospho-extracellular signal–regulated kinase
FGFR 1/2/3 = fibroblast growth factor receptor 1, 2 and 3
~~FGF23 = fibroblast growth factor 23~~

~~* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877 only for Cycle 1.~~

….

New text:

Table 16-7: Parameters and time points for biomarker investigations in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)

Parameters	PRE-TREATMENT		TREATMENT					FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycles 1-12 Day 1	Day 8	Day 15	Cycles ≥13 Day 1	Day 11	EOT visit
Tumor tissue:								
p-ERK1/2 levels		X[A]	X[B] only Cycle 2					
FGFR1/2/3 expression	X[C]							
FGFR and FGFR pathway mutations	X[C]							

p-ERK = phospho-extracellular signal–regulated kinase
FGFR 1/2/3 = fibroblast growth factor receptor 1, 2 and 3
….

15.5.2.31 16.8 Response evaluation criteria in solid tumors (RECIST v1.1)

This section was changed as a result of Modification 6.

Old text:

…

Table 14-10: Target and non-target lesion response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
CR	CR	No	CR	4 ~~6~~ weeks Confirmation
CR	Non-CR/Non-PD	No	PR	4 ~~6~~ weeks Confirmation
CR	Not evaluated	No	PR	4 ~~6~~ weeks Confirmation
PR	Non-PD or not all evaluated	No	PR	4 ~~6~~ weeks Confirmation
…				

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease;

Subjects with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 14-11: Time-point response: Subjects with non-target disease only

Non-Target Lesions	New Lesions	Overall Response	Best Response also Requires
CR	No	CR	4 ~~6~~ weeks Confirmation
…			

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

a: ‘Non-CR/non-PD’ is preferred over ‘SD’ for non-target disease because SD is increasingly used as an endpoint for assessment of efficacy in some trials, therefore, to assign this category when no lesions can be measured is not advised.

New text:

Table 16-10: Target and non-target lesion response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
CR	CR	No	CR	not earlier than 4 weeks Confirmation
CR	Non-CR/Non-PD	No	PR	not earlier than 4 weeks Confirmation
CR	Not evaluated	No	PR	not earlier than 4 weeks Confirmation
PR	Non-PD or not all evaluated	No	PR	not earlier than 4 weeks Confirmation
…				

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease;

Subjects with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 16-11: Time-point response: Subjects with non-target disease only

Non-Target Lesions	New Lesions	Overall Response	Best Response also Requires
CR	No	CR	not earlier than 4 weeks Confirmation
…			

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

a: ‘Non-CR/non-PD’ is preferred over ‘SD’ for non-target disease because SD is increasingly used as an endpoint for assessment of efficacy in some trials, therefore, to assign this category when no lesions can be measured is not advised.

15.6 Amendment 7

Date of amendment: 16 March 2017

15.6.1 Overview of changes

15.6.1.1 Modification 1: Change in Medical Expert and further clarifications

Description of modification to the study plan

The medical expert for this study changed. Moreover, minor changes were done for clarification.

Rationale for introducing the modification

Due to organizational reasons the medical expert for this study was changed.

List of CSP sections affected by this modification

Sections 1, 5 and 16.3

15.6.1.2 Modification 2: Safety cohort

Description of modification to the study plan

A 3rd study part investigating the "Safety cohort" was included.

Rationale for introducing the modification

Preliminary safety data of patients with advanced cancer treated with BAY 1163877 showed a favorable safety profile (details can be found in the current version of the IB). However, sample size is still limited in selected indications (sqNSCLC, LAC, BC) and additional safety data will be generated in Study Part 3 "Safety cohort".

In parallel, changes of selected immune parameters will be assessed in Part 3. It was shown that FGFR3 expression is inversely correlated to PD-L1 expression in tumor tissue of patients with BC. This finding was confirmed in archival biopsy samples collected in study 16443. A similar correlation was detected in patients with sqNSCLC and LAC. It is assumed that a causal relationship between FGFR expression and T-cell exclusion leads to low PD-L1 levels. Potentially, inhibition of FGFR can overcome this interaction and render tumors targetable by the immune system. Preclinical models are not available due to limitations in mimicking immune responses in murine model systems.

List of CSP sections affected by this modification

Sections 2, 3, 4, 6, 6.2, 7.1.1.1, 7.1.1.2, 7.1.2.2, 7.1.2.3, 8.1, 8.4.2, 8.4.2.1, 8.7, 9.1.2.1.1, 9.1.2.1.2, 9.1.2.3.1, 9.1.2.3.2, 9.4.1.2, 9.4.4.1, 9.5.4.2, 10.7, 13.2, 14, 16.1 and 16.2.

15.6.1.3 Modification 3: Modifications of the criteria for dose modification and withdrawal and minor clarification/general instructions

Description of modification to the study plan

Changes done by the local Amendment 6 were included.

Liver toxicity criteria were modified and criteria for retinal detachment were added.

The protocol was modified to clarify that tissue mineralization and increased Ca x PO4 are different events. Furthermore investigators were instructed to carefully monitor patients with a GFR in the range of 30 mL/ min to 60 mL/min. Conditions when patients may continue treatment although they show disease progression were clarified. Possible drug interaction with respect to BCRP and/or P-gp was addressed.

Rationale for introducing the modification

Modifications were implemented to further reduce the risk of drug-induced toxicities.

List of CSP sections affected by this modification

Sections 7.2.1, 8.4.3, 8.9.3 and 9.1.2.3.

15.6.2 Changes of protocol

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment. Deletions are crossed out in the "old text". Additions are underlined in the "new text". Corrections of typing errors, omissions or terminology (minor corrections) are not highlighted in this amendment.

15.6.2.1 Title page

This section was changed as a result of Modification 1.

Old text:

Sponsor's medical expert:	PPD Bayer ~~Pharma~~ AG Muellerstrasse 178, 13353 Berlin, Germany Phone No: PPD

New text:

Sponsor's medical expert:	PPD Bayer AG Muellerstrasse 178, 13353 Berlin, Germany Phone No: PPD

Signature of the sponsor's medically responsible person

Old text:

PPD

Name	Role

New text:

PPD

Name	Role

15.6.2.2 Section 2 Synopsis

This section was changed as a result of Modification 2.

Old text:

Diagnosis and main criteria for inclusion	Eligibility criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 1 and Part 2) … • Subjects with histologically or cytologically confirmed, refractory, locally advanced or metastatic solid tumors (all comer for study Part1; sqNSCLC, LAC, BC) who are not candidates for standard therapy. … Subjects enrolled in the MTD expansion cohorts of Study Part 1 and Part 2 must present high FGFR expression levels based on archival or fresh tumor biopsy specimen analysis. … **(only for MTD expansion cohorts of study Part 1 (all comer) and Part 2 (sqNSCLC + LAC +BC + SCCHN))** **…** Note: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. …

Methodology	**…** Note: Treatment with BAY 1163877 at MTD in Part 1 (expansion cohort "all comer"), Part 2 (expansion cohort "sqNSCLC + LAC + BC + SCCHN") can run in parallel. … At home, subjects will document the intake of study drug (date and time of dosing as well as the administered dose) on a compliance sheet / paper diary (source document to verify treatment compliance). The complete duration of the study (Part 1 and Part 2) depends on the number of dose-escalation steps in Part 1 and will be approximately 7 years. … **Pharmacokinetics PK):** … In the MTD expansion cohorts, in ~~a maximum of~~ 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated formula), serial PK blood samples will be collected on Cycle 1 Day 1 and Day 15. … **Safety / tolerability:** Safety will be assessed by close monitoring and timely assessment of adverse events (AEs), laboratory parameters (blood tests, urinalysis), vital signs (blood pressure, heart rate), subject's medical condition (physical examination including weight), ~~vision tests,~~ general well-being and activities of daily life (Eastern Cooperative Oncology Group (ECOG) performance status). … **Biomarker analysis in tumor tissue** Biomarker analysis will be done at screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN) according to FGFR expression levels / FGFR mutation using either an archival or fresh tumor biopsy material (see inclusion criteria).

	Analysis of phospho-extracellular signal-regulated kinase 1/2 levels, (p-ERK1/2) will be done at screening and on Cycle 2, Day 1 for all subjects who are willing to undergo a biopsy both at screening and on Cycle 2, Day 1. …
Number of subjects	• *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)*: Additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and a cohort of ~~approximately~~ 30 evaluable subjects with BC and at least 8 subjects with SCCHN treated at MTD.

New text:

Study objective(s)	**Exploratory objectives** To evaluate selected immune parameters
Dose(s)	*Study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC):* • Subjects receive the MTD of BAY 1163877 determined in study Part 1.
Duration of treatment	Duration and dosing schedule for subjects of study Part 3: Subjects will receive BAY 1163877 twice daily from Cycle 1, Day 1 ongoing. Evidence of tumor progression, unacceptable toxicity, consent withdrawal or subject's withdrawal from the study at the discretion of the Investigator may lead to termination of treatment.
Diagnosis and main criteria for inclusion	Eligibility criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 1, Part 2, and Part 3) … • Subjects with histologically or cytologically confirmed, refractory, locally advanced or metastatic solid tumors (all comer for study Part1; sqNSCLC, LAC, BC or SCCHN for Part 2; sqNSCLC, LAC, or BC for Part 3) who are

	not candidates for standard therapy. … • Subjects enrolled in the MTD expansion cohorts of Study Part 1, Part 2, and Part 3 must present high FGFR expression levels based on archival or fresh tumor biopsy specimen analysis. … (**only for MTD expansion cohorts of study Part 1 (all comer), Part 2 (sqNSCLC + LAC +BC + SCCHN) and Part 3 (sqNSCLC + LAC + BC)** … Note: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy for biomarker (p-ERK1/2) studies is taken. … • **Only for study Part 3:** Subjects consent to undergo a paired biopsy at screening and between Cycle 2, Day 1 and Cycle 2, Day 21
Study design	Study Part 3 will expand the safety database and in parallel will collect additional efficacy data and explore changes of selected immune parameters during treatment with BAY 1163877 at the MTD identified in Part 1 in subjects with sqNSCLC, LAC, and BC.
Methodology	*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"), and Part 2 (expansion cohort "sqNSCLC + LAC + BC + SCCHN") and Part 3 (expansion cohort "Safety cohort", sqNSCLC + LAC + BC) can run in parallel. … At home, subjects will document the intake of study drug (date and time of dosing as well as the administered dose) on a compliance sheet / paper diary

(source document to verify treatment compliance). 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.

Pharmacokinetics (PK)

…

In all subjects participating in Study Part 3, multiple dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day 15 (up to 12 hours after dosing).

…

In the MTD expansion cohorts, in approximately 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated formula), serial PK blood samples will be collected on Cycle 1 Day 1 and Day 15.

…

Safety / tolerability: Safety will be assessed by close monitoring and timely assessment of adverse events (AEs), laboratory parameters (blood tests, urinalysis), vital signs (blood pressure, heart rate), subject's medical condition (physical examination including weight), ophtalmological examination, general well-being and activities of daily life (Eastern Cooperative Oncology Group (ECOG) performance status).

…

Biomarker analysis in tumor tissue

…

Biomarker analysis will be done at screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN; Part 3: *"Safety cohort" sqNSCLC + LAC + BC*) according to FGFR expression levels / FGFR mutation using either an archival or fresh tumor biopsy material (see inclusion criteria).

Analysis of phospho-extracellular signal-regulated kinase 1/2 levels, (p-ERK1/2) will be done at screening

	and on Cycle 2, Day 1 for all subjects of study Part 1 and Part 2 who are willing to undergo a biopsy both at screening and on Cycle 2, Day 1. Priming of immune response (only in Part 3 "Safety cohort"): Selected parameters of immune response will be measured in fresh tumor tissue at baseline and between Cycle 2, Day 1 and Cycle 2, Day 21 and peripheral blood at the following timepoints: at baseline; Cycle 1, Day 8; Cycle 2, Day 1; Cycle 2, Day 15; and on the day of the second biopsy.
Number of subjects	• *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)*: Additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and a cohort of at least 30, up to a 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.

15.6.2.3 Section 3 Introduction

This section was changed as a result of Modification 2.

Rationale of the study

Additional text:

It was shown that FGFR3 expression is inversely correlated to programmed death-ligand 1 (PD-L1) expression and T cell infiltration in tumor tissue of patients with BC(40). This finding was confirmed in archival biopsy samples collected in study 16443. A similar correlation was detected in patients with sqNSCLC and LAC in study 16443.

It is assumed that a causal relationship between FGFR expression and T cell exclusion leads to low PD-L1 levels and decreased responsiveness towards inhibition of the PD-L1 axis. Potentially, inhibition of FGFR can overcome this interaction and render tumors targetable by the immune system.

Immune responses and the tumor microenvironment are inadequately reflected in preclinical cancer models. We therefore aim to analyze selected immune parameters before and during BAY1163877 treatment in paired biopsies and in serum of biomarker-selected patients. Fresh tumor tissue will be used to assess immune parameters indicating a T cell response against the tumor tissue. This will be done by performing gene expression

profiling (nCounter PanCancer Immune Profiling Panel) and immunohistochemistry for CD8+ T cell infiltration and PD-L1 expression on the tumor tissue. Peripheral blood will be used to collect serum to determine cytokine levels (IL-6, IFN-gamma, and other cytokines if needed). Aim of the assessment of peripheral blood is to search for changes in this easily accessible specimen that reflect the immune response in the tumor tissue.

15.6.2.4 Section 4 Study objectives

This section was changed as a result of Modification 2.

New text:

Exploratory objective:

- To evaluate selected immune parameters.

15.6.2.5 Section 5 Investigator (s) and other study participants

This section was changed as a result of Modification 1.

Old text:

Sponsor's Medical Expert

Name:	PPD
Title:	PPD
Address:	Bayer ~~Pharma~~ AG
	Muellerstr, 178
	13353 Berlin, Germany
Telephone No:	PPD
~~Fax No:~~	PPD

New text:

Sponsor's Medical Expert

Name:	PPD
Title:	PPD
Address:	Bayer AG
	Muellerstr, 178
	13353 Berlin, Germany
Telephone No:	PPD

15.6.2.6 Section 6 Study design

This section was changed as a result of Modification 2.

Old text:

Design overview

…

- *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)*: additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and ~~approximately~~ 30 evaluable subjects with BC and at least 8 subjects with SCCHN treated at MTD.

…

The complete duration of the study (Part 1, and Part 2) depends on the number of dose-escalation steps in Part 1 and will be approximately 7 years.10

…

PK assessments will be performed in all subjects participating in study Part 1 / dose escalation and MTD expansion (all comer). 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 ~~a maximum of~~ 8 subjects of the MTD expansion cohorts with impaired renal function at baseline.

…

All subjects participating in either of the ~~2~~ MTD expansion cohorts (Part 1 and Part 2) will have 2 PK samples drawn for the purpose of exposure-response modeling 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).

Figure 6-1: 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.

…

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

…

- Treatment ….

Note: Treatment with BAY 1163877 at MTD in Part 1 (expansion cohort “all comer”) and

Part 2 (expansion cohort "sqNSCLC + LAC + BC + SCCHN") can run in parallel.

…

Treatment: Subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects of study Part 2 and ~~a maximum of~~ 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 "drug-free day" (to enable single dose PK assessments).

…

Pharmacokinetics (PK): …

In the MTD expansion cohorts, in ~~a maximum of~~ 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated formula), serial PK blood samples will be collected on Cycle 1 Day 1 and Day 15.

…

Safety /tolerability: ….

Safety will be assessed by close monitoring and timely assessment of adverse events (AEs), laboratory parameters (blood tests, urinalysis), vital signs (blood pressure, heart rate), subject's medical condition (physical examination including weight), ~~vision tests,~~ general well-being and activities of daily life (Eastern Cooperative Oncology Group (ECOG) performance status).

…

Pharmacodynamic (PD) biomarkers: …

Biomarker analysis in tumor tissue: Biomarker analysis will be done at screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN) according to FGFR expression levels / FGFR mutation using either an archival tumor tissue specimen or fresh tumor biopsy material (see Section 7.1.1, inclusion criteria).

Analysis of phospho-extracellular signal-regulated kinase 1/2 levels, (p-ERK1/2) will be done at screening and on Cycle 2, Day 1 for all subjects who are willing to undergo a biopsy both at screening and on Cycle 2, Day 1.

New text:

Design overview

…

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, and Part 2, and Part 3) depends on the number of dose-escalation steps in Part 1 and will be approximately 7 years.

…

- *Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)*: additional subjects will be enrolled to have 20 evaluable subjects with sqNSCLC or LAC and of at least 30, up to a 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.

…

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 modeling 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.

Figure 6-1: 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,Part 2, or Part 3 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.

…

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

…

- Treatment

…

  - *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.

…

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 "drug-free 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").

…

Pharmacokinetics (PK): …

In the MTD expansion cohorts, in approximately 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated formula), serial PK blood samples will be collected on Cycle 1 Day 1 and Day 15. In all subjects participating in Study Part 3/"Safety cohort", multiple dose PK of BAY 1163877 will be evaluated in plasma samples collected on Cycle 1, Day 15.

…

Safety /tolerability: ….

Safety will be assessed by close monitoring and timely assessment of adverse events (AEs), laboratory parameters (blood tests, urinalysis), vital signs (blood pressure, heart rate), subject's medical condition (physical examination including weight), ophthalmological examination, general well-being and activities of daily life (Eastern Cooperative Oncology Group (ECOG) performance status).

…

Assessment of immune priming (Part 3): Selected parameters of immune response will be measured in fresh tumor tissue at baseline and again between Cycle 2, Day 1 and Cycle 2, Day 21; and in peripheral blood at the following timepoints: at baseline; Cycle 1, Day 8; Cycle 2, Day 1; Cycle 2, Day 15; and on the day of the second biopsy.

Fresh tumor tissue will be used to assess immune parameters indicating a T cell response against the tumor tissue. This will be done by performing gene expression profiling (nCounter PanCancer Immune Profiling Panel) and immunohistochemistry for CD8+ T cell infiltration and PD-L1 expression on the tumor tissue. Peripheral blood will be used to collect serum to determine cytokine levels (IL-6, IFN-gamma, and other cytokines if

needed). Aim of the assessment of peripheral blood is to search for changes in this easily accessible specimen that reflect the immune response in the tumor tissue.

…

Pharmacodynamic (PD) biomarkers: …

Biomarker analysis in tumor tissue: Biomarker analysis will be done at screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN; Part 3: sqNSCLC + LAC + BC) according to FGFR expression levels / FGFR mutation using either an archival tumor tissue specimen or fresh tumor biopsy material (see Section 7.1.1, inclusion criteria).

Analysis of phospho-extracellular signal-regulated kinase 1/2 levels, (p-ERK1/2) will be done at screening and on Cycle 2, Day 1 for all subjects of study Part 1 and Part 2 who are willing to undergo a biopsy both at screening and on Cycle 2, Day 1.

15.6.2.7 Section 6.2 Justification of the design

This section was changed as a result of Modification 2.

New text:

Study Part 3 / "Safety cohort" (sqNSCLC + LAC + BC)

Preliminary safety data of patients with advanced cancer treated with BAY 1163877 showed a favorable safety profile (details can be found in the current version of the IB). However, sample size is still limited in selected indications (sqNSCLC, LAC, BC) and additional safety data will be generated in Study Part 3 "Safety cohort". In parallel, additional efficacy data will be collected and changes of selected immune parameters will be assessed in Part 3.

It was shown that FGFR3 expression is inversely correlated to programmed death-ligand 1 (PD-L1) expression and T cell infiltration in tumor tissue of patients with BC (40). This finding was confirmed in archival biopsy samples collected in study 16443. A similar correlation was detected in patients with sqNSCLC and LAC in study 16443.

Recently, the PD1 and PD-L1 inactivating antibodies received accelerated approval by the FDA for patients with BC. It was demonstrated that patients with a low expression of PD-L1 had a smaller chance to respond to atezolizumab treatment.

It is assumed that a causal relationship between FGFR expression and T cell exclusion leads to low PD-L1 levels and decreased responsiveness towards inhibition of the PD-L1 axis. Potentially, inhibition of FGFR can overcome this interaction and render tumors targetable by the immune system.

Immune responses and the tumor microenvironment are inadequately reflected in preclinical cancer models. We therefore aim to analyze selected immune parameters before and during BAY1163877 treatment in paired biopsies and in serum of biomarker-selected cancer patients. Fresh tumor tissue will be used to assess immune parameters indicating a T cell response against the tumor tissue. This will be done by performing gene expression profiling (nCounter PanCancer Immune Profiling Panel) and

immunohistochemistry for CD8+ T cell infiltration and PD-L1 expression on the tumor tissue. Peripheral blood will be used to collect serum to determine cytokine levels (IL-6, IFN-gamma, and other cytokines if needed). Aim of the assessment of peripheral blood is to search for changes in this easily accessible specimen that reflect the immune response in the tumor tissue.

15.6.2.8 Section 7.1.1.1 Eligibility criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 1 and Part 2)

This section was changed as a result of Modification 2.

Old text:

7.1.1.1 Eligibility criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 1 and Part 2)

…

- Subjects with histologically or cytologically confirmed, refractory, locally advanced or metastatic solid tumors (all comer for study Part1; sqNSCLC, LAC, BC or SCCHN for Part 2) who are not candidates for standard therapy.

New text:

7.1.1.1 Eligibility criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 1, Part 2 and Part 3)

…

- Subjects with histologically or cytologically confirmed, refractory, locally advanced or metastatic solid tumors (all comer for study Part1; sqNSCLC, LAC, BC or SCCHN for Part 2; sqNSCLC, LAC, or BC for Part 3) who are not candidates for standard therapy.

15.6.2.9 Section 7.1.1.2 Eligibility criteria for study treatment

This section was changed as a result of Modification 2.

Old text:

- Subjects enrolled in the MTD expansion cohorts of Study Part 1 and Part 2 must present high FGFR expression levels based on archival or fresh tumor biopsy specimen analysis.
Bladder cancer subjects with low overall FGFR expression levels can be included if activating FGFR3 mutations are confirmed.
(only for MTD expansion cohorts of study Part 1 (all comer) and Part 2 (sqNSCLC + LAC +BC + SCCHN))

…

Note: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or

monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker ~~(p-ERK1/2)~~ studies.

New text:

- Subjects enrolled in the MTD expansion cohorts of Study Part 1, Part 2 and Part 3 must present high FGFR expression levels based on archival or fresh tumor biopsy specimen analysis.
Bladder cancer subjects with low overall FGFR expression levels can be included if activating FGFR3 mutations are confirmed.
(only for MTD expansion cohorts of study Part 1 (all comer), Part 2 (sqNSCLC + LAC +BC + SCCHN) and Part 3 (sqNSCLC + LAC + BC)).

….

Note: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy for biomarker (p-ERK1/2) studies is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

…

- Subjects consent to undergo paired biopsies at screening and between Cycle 2, Day 1 and Cycle 2, Day 21
(only for Study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC))

15.6.2.10 Section 7.1.2.2 Exclusion criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 2)

This section was changed as a result of Modification 2.

Old section heading:

Exclusion criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 2)

New section heading:

Exclusion criteria for FGFR expression / FGFR mutation testing (only for MTD expansion cohorts of study Part 2 and Part 3)

15.6.2.11 Section 7.1.2.3 Exclusion criteria

This section was changed as a result of Modification 2.

Old text:

- FGFR testing shows low FGFR expression levels
(only for MTD expansion cohorts of study Part 1 (all comer) and Part 2 (sqNSCLC + LAC + SCCHN))

- No consent for mandatory paired biopsies for biomarker

(only for MTD expansion cohorts of study Part 1 (all comer))

- FGFR expression / FGFR mutation testing shows low FGFR expression levels and absence of activating mutation in FGFR3 gene
(only for Part 2 (BC))

…

New text:

- FGFR testing shows low FGFR expression levels
(only for MTD expansion cohorts of study Part 1 (all comer), Part 2 (sqNSCLC + LAC + SCCHN) and Part 3 (sqNSCLC + LAC))

- No consent for mandatory paired biopsies for biomarker (Part 1) or assessment of immune parameters (Part 3)
(only for MTD expansion cohorts of study Part 1 (all comer) and study Part 3 (sqNSCLC+ LAC + BC)

- FGFR expression / FGFR mutation testing shows low FGFR expression levels and absence of activating mutation in FGFR3 gene
(only for Part 2 and Part 3 (BC))

…

15.6.2.12 Section 7.2.1 Withdrawal

This section was changes as a result of Modification 3.

Old text

- Tumor progression

Subjects with documented disease progression, unless the investigator (in consultation with the sponsor) deems that continued treatment is appropriate.

New text:

- Retinal detachment of grade 2 or higher according to CTCAE v4.03
- AST/ALT > 3xULN with concomitant bilirubin > 2xULN in the absence of another reason for these elevations
- AST/ALT > 8xULN or AST/ALT > 5xULN for > 2 weeks if no other reason is found for these elevations

- Tumor progression
  - Subjects with documented disease progression, unless the investigator (in consultation with the sponsor) deems that continued treatment is appropriate. Patients may continue if they experience clinical benefit as assessed by the investigator, do not exhibit rapid disease progression and have stable performance status. In addition, treatment beyond progression should not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases).

15.6.2.13 Section 8.1 Treatments to be administered

This section was changed as a result of Modification 2.

New text:

Investigational medicinal product (IMP) – test drug

In study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC), subjects will be treated with the MTD of BAY 1163877 determined in study Part 1.

15.6.2.14 Section 8.4.2 Selection and timing of dose for each subject

This section was changed as a result of Modification 2.

Old text:

Extent and duration of drug exposure of the individual subject in study Part 2 / dose expansion (sqNSCLC + LAC + BC + SCCHN) are given in Section 6.

New text:

Extent and duration of drug exposure of the individual subject in study Part 2 / dose expansion (sqNSCLC + LAC + BC + SCCHN) and study Part 3 / dose expansion "Safety cohort" (sqNSCLC + LAC + BC) are given in Section 6.

15.6.2.15 8.4.2.1 Dosing schedule

This section was changed as a result of Modification 2.

New text:

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

- Subjects will receive BAY 1163877 twice daily from Cycle 1, Day 1 ongoing.

15.6.2.16 8.4.3 Dose modification and delays

This section was changed as a result of Modification 3.

Old text:

Liver toxicity

Table 8-6: Dose modifications of BAY 1163877 for liver toxicity

a	~~If all values remain stable for 2 cycles, dose re-escalation may be considered at the discretion of the investigator. After re-escalation, AST, ALT, and bilirubin should be checked weekly for at least 4 weeks.~~

~~Tissue mineralization~~

Dose modifications of BAY 1163877 for ~~tissue mineralization~~ are presented in Table 8-7. ~~Tissue mineralization refers~~ to Ca x PO4 ≥ 70 mg²/dL² considered possibly related to BAY 1163877.

Table 8-7: Dose modifications of BAY 1163877 for ~~tissue mineralization~~

Toxicity	Modification schedule
Ca x PO4 (≥ 70 mg²/dL²)	Hold BAY 1163877, treat with phosphate chelators until recovery, to Ca x PO4 < 70 mg²/dL². Resume same dose level, continue phosphate chelators and check weekly for at least 4 weeks.
- 1st reappearance	Hold BAY 1163877, treat with phosphate chelators until recovery to Ca x PO4 < 70 mg²/dL², then reduce 1 dose level, continue phosphate chelator and check weekly for at least 4 weeks.
- 2nd reappearance	Hold BAY 1163877 until recovery to Ca x PO4 < 70 mg²/dL², then reduce 1 additional dose level, continue phosphate chelators and check weekly for at least 4 weeks.
- 3rd reappearance	Withdraw subject from study treatment.

…

New text:

…

Table 8-6: Dose modifications of BAY 1163877 for liver toxicity

a Dose will not be re-escalated after dose reduction for toxicity.

Patients with AST/ALT > 3xULN with concomitant bilirubin > 2xULN in the absence of another reason for these elevations have to permanently discontinue study drug. Permanent discontinuation also applies to patients with AST/ALT > 8xULN or AST/ALT > 5xULN for > 2 weeks if no other reason is found for these elevations.

Increased Ca x PO4

Dose modifications of BAY 1163877 for Ca x PO4 ≥ 70 mg²/dL² considered possibly related to BAY 1163877 are presented in Table 8-7.

Table 8-7: Dose modifications of BAY 1163877 for increased Ca x PO4

Toxicity	Modification schedule
Ca x PO4 (≥ 70 mg²/dL²)	Hold BAY 1163877, treat with phosphate chelators and check twice weekly until recovery, to Ca x PO4 < 70 mg²/dL². Resume same dose level, continue phosphate chelators and check tweekly for at least 4 weeks.
- 1st reappearance	Hold BAY 1163877, treat with phosphate chelators and check twice weekly until recovery to Ca x PO4 < 70 mg²/dL², then reduce 1 dose level, continue phosphate chelator and check weekly for at least 4 weeks.
- 2nd reappearance	Hold BAY 1163877 and check twice weekly until recovery to Ca x PO4 < 70 mg²/dL², then reduce 1 additional dose level, continue phosphate chelators and check weekly for at least 4 weeks.
- 3rd reappearance	Withdraw subject from study treatment.

…

In patients with hyperphosphatemia (Ca x PO4 ≥ 70 mg²/dL²), the serum phosphate and calsium levels have to be checked twice weekly until resolution (Ca x PO4 < 70 mg²/dL²).

In patients with hypocalcemia, an additional 12-lead ECG has to be obtained on the day of detection of hypocalcemia.

Retinal detachment

Patients that experience retinal detachment of grade 2 or higher according to CTCAE v4.03 have to be permanently discontinued from study treatment.

15.6.2.17 Section 8.7 Treatment compliance

This section was changed as a result of Modification 2.

Old text:

A compliance of at least 80% is required, meaning documented intake of at least 80% of the planned study medication (80 % = 32 doses or 16 days in Cycle 1 with PK assessment and 34 doses or 17 days in ≥ Cycles 2 and in Cycle 1 without PK assessment.

New text:

A compliance of at least 80% is required, meaning documented intake of at least 80% of the planned study medication (80 % = 32 doses or 16 days in Cycle 1 with PK assessment [Part 1 and Part 2 only] and 34 doses or 17 days in ≥ Cycles 2 and in Cycle 1 without PK assessment [including Part 3]).

15.6.2.18 Section 8.9.3 Permitted concomitant therapy

This section was changed as a result of Modification 3.

New text:

- In view of the maximum dose of 800 mg b.i.d., a risk for clinically relevant drug interaction due to inhibition of BCRP and/or P-gp in the intestine for drugs with a low bioavailability limited by P-gp and BCRP cannot be ruled out. However, based on the maximum achievable plasma BAY 1163877 concentration, risk of clinically relevant drug interaction due to systemic inhibition of BCRP and P-gp is regarded as low.

15.6.2.19 Section 9.1.2.1.1 FGFR expression / FGFR mutation testing (MTD expansion cohorts only)

This section was changed as a result of Modification 2.

Old text:

A separate subject information sheet / informed consent form (SIS / ICF) for FGFR expression / FGFR mutation testing must be signed by all subjects recruited for study Part 1 or Part 2 MTD expansion cohort (see Section 13.2).

New text:

A separate subject information sheet / informed consent form (SIS / ICF) for FGFR expression / FGFR mutation testing must be signed by all subjects recruited for study Part 1, Part 2 MTD expansion cohort or Part 3 (see Section 13.2).

15.6.2.20 Section 9.1.2.1.2 Screening

This section was changed as a result of Modification 2.

Old text:

- Demographic data (already collected for subjects of Part 1 or Part 2 MTD expansion cohorts, see Section 9.1.2.1.1)

- Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report (already done for subjects of Part 1 or Part 2 MTD expansion cohorts, see Section 9.1.2.1.1)

- Complete medical / oncological history, TNM classification (see Section 9.2.3) (already done for subjects of Part 1 or Part 2 MTD expansion cohorts, see Section 9.1.2.1.1)

…

- ECOG performance status assessment (also for subjects of Part 1, Part 2 MTD expansion cohorts, see Section 9.1.2.1.1)

…

Note 1: A biopsy is mandatory for all subjects in the MTD expansion cohort of Part 1 and Part 2 for whom no archival biopsy is available for FGFR expression / FGFR mutation testing. …

Note 2: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken….

New text:

Within 28 Days Prior to First Dose of BAY 1163877

- Demographic data (already collected for subjects of Part 1, Part 2 or Part 3 MTD expansion cohorts, see Section 9.1.2.1.1)
- Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report (already done for subjects of Part 1, or Part 2 or Part 3 MTD expansion cohorts, see Section 9.1.2.1.1)
- Complete medical / oncological history, TNM classification (see Section 9.2.3) (already done for subjects of Part 1, Part 2 or Part 3 MTD expansion cohorts, see Section 9.1.2.1.1)

…

- ECOG performance status assessment (also for subjects of Part 1, Part 2 or Part 3 MTD expansion cohorts, see Section 9.1.2.1.1)

…

- Obtain pre-treatment biopsy:

  …

  - mandatory for all subjects in the study Part 3 / MTD expansion cohort "Safety cohort" (sqNSCLC + LAC + BC)
  - Note 1: A biopsy is mandatory for all subjects in the MTD expansion cohort of Part 1, Part 2 and Part 3 for whom no archival biopsy is available for FGFR expression / FGFR mutation testing.
  - Note 2: Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy for biomarker (p-ERK1/2) studies is taken….

Within 7 Days Prior to First Dose of BAY 1163877

…

- *Only for subjects in Part 3:* peripheral blood sample collection for determination of cytokine levels in serum.

15.6.2.21 Section 9.1.2.3 Treatment

This section was changed as a result of Modification 3.

New text:

…

Patients with an estimated GFR in the range 30 mL/ min to 60 mL/min should be carefully monitored for signs of increased toxicity.

15.6.2.22 Section 9.1.2.3.1 Cycle 1

This section was changed as a result of Modification 2.

Old text

Day 1

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and ~~a maximum of~~ 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)

…

→ Oral administration of BAY 1163877 (single dosing for subjects with PK assessment, twice daily dosing for subjects without PK assessment

Day 2

No administration of BAY 1163877 ("drug-free day") for subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects with PK assessment in study Part 2 and ~~a maximum of~~ 8 subjects with PK assessment in the MTD expansion cohorts with impaired renal function at baseline [including "food effect assessment"])

- **Twice daily administration of BAY 1163877** for subjects without PK assessment (remaining subjects of study Part 2)

…

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and ~~a maximum of~~ 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)

…

Day 3

…

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and ~~a maximum of~~ 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)

…

Days 15 (Visit)

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and ~~a maximum of~~ 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)

New text

Day 1

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and approximately 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)

→ Oral administration of BAY 1163877 (single dosing for subjects with PK assessment, twice daily dosing for subjects without PK assessment and for subject in Part 3)

Day 2

No administration of BAY 1163877 ("drug-free day") for subjects with PK assessment (all subjects of study Part 1 and at least 12 subjects with PK assessment in study Part 2 and approximately 8 subjects with PK assessment in the MTD expansion cohorts with impaired renal function at baseline [including "food effect assessment"])

- **Twice daily administration of BAY 1163877** for subjects without PK assessment (remaining subjects of study Part 2) and for subjects of Part 3

…

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and approximately 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)

…

Day 3

…

- PK sampling (all subjects of study Part 1 and at least 12 subjects of study Part 2 and approximately 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)

…

Day 8±1 (Visit)

- *Only for subjects in Part 3:* Collection of peripheral blood for determination of cytokine levels

…

Days 15 (Visit)

- PK sampling (all subjects of study Part 1, 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)

15.6.2.23 Section 9.1.2.3.2 Subsequent Cycles (Cycles 2-12)

This section was changed as a result of Modification 2.

Old text:

Day 1 (Visit)

- Only on Day 1 of Cycles 2, 3, 4 and 5: Blood (plasma) sample collection for exposure-response modelling at pre-dose and between 0.5 and 1.5 hours post-dose in all subjects participating in the MTD expansion cohorts of study Part 1 and part 2 , see Table 16-3. The dose needs to be taken under supervision and the time recorded.

- Only on Day 1 of Cycle 2: Obtain second biopsy: mandatory for all subjects in the MTD expansion cohort of Part 1 (all comer), voluntary for ~~all other subjects~~, and send to laboratory, see Section 16.2.

-

New text:

Day 1 (Visit)

- *Only for subjects in Part 3 in Cycle 2:* peripheral blood sample collection for determination of cytokine levels.

- Only on Day 1 of Cycles 2, 3, 4 and 5: Blood (plasma) sample collection for exposure-response modelling at pre-dose and between 0.5 and 1.5 hours post-dose in all subjects participating in the MTD expansion cohorts of study Part 1, Part 2, and Part 3 , see Table 16-3 (not in subjects with impaired renal function). The dose needs to be taken under supervision and the time recorded.

- Only on Day 1 of Cycle 2: Obtain second biopsy: mandatory for all subjects in the MTD expansion cohort of Part 1 (all comer), voluntary for subjects in the dose escalation cohorts of study Part 1 (all comer) and in the MTD expansion cohort of Part 2, and send to laboratory, see Section 16.2.

- Mandatory for all subjects in study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC): Between Day 1 and Day 21 of Cycle 2: Obtain second biopsy and send to laboratory, see Section 16.2; obtain peripheral blood for determination of cytokine levels. Subjects in Part 3 will provide one PK sample within 1 hour of biopsy collection in Cycle 2.

…

Day 8 ± 1 and Day 15 ± 1 (Visits)

- *Only for subjects in Part 3 on Day 15 in Cycle 2:* peripheral blood sample collection for determination of cytokine levels.

15.6.2.24 Section 9.4.1.2 Assessment of immune priming

This section was added as a result of Modification 2.

New text:

Assessment of immune response will be done at screening and during treatment for subjects in the "Safety cohort" (Part 3: sqNSCLC + LAC + BC). For gene expression profiling (nCounter PanCancer Immune Profiling Panel) and immunohistochemistry for CD8+ T cell infiltration and PD-L1 expression afresh tumor biospy (e.g. obtained by endoscopic or ultrasound guided biopsy) will be collected as follows:

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

  Screening: Biopsy is mandatory

  Between Cycle 2, Day 1 and Cycle 2, Day 21: Biopsy is mandatory

Peripheral blood will be collected for determination of cytokine levels (IL-6, IFN-gamm, and others if needed) at the following timepoints: at baseline; Cycle 1, Day 8; Cycle 2, Day 1; Cycle 2, Day 15; and on the day of the second biopsy..

15.6.2.25 Section 9.4.2.1 Drug measurement

This section was changed as a result of Modification 2.

Old text:

… In the MTD expansion cohorts pharmacokinetic assessments will be performed in ~~a total of~~ 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated formula).

New text:

… In the MTD expansion cohorts pharmacokinetic assessments will be performed in approximately 8 subjects with moderately impaired renal function at baseline (glomerular filtration rate [GFR] of 30 to 59 mL/min/1.73 m^2 according to the modified diet in renal disease [MDRD] abbreviated formula). In all subjects participating in study Part 3/ MTD expansion "Safety cohort", multiple dose pharmacokinetics (on Cycle 1 Day 15) will be performed.

…

- Cycle 2: Subjects in Part 3/ MTD expansion "Safety cohort" will provide one PK sample within 1 hour of biopsy collection in Cycle 2.

15.6.2.26 Section 9.4.4 Biomarker investigation

Old text:

…

Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken….

New text:

Biomarker analysis will be done at pre-screening for subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN; Part 3 sqNSCLC + LAC + BC) according to FGFR expression levels / FGFR mutation using either an archival tumor tissue specimen or fresh tumor biopsy material (see Section 7.1.1: Inclusion criteria, and Section 9.4.4.1: Predictive marker investigation).

….

Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy for biomarker (p-ERK1/2) studies is taken….

15.6.2.27 Section 9.4.4.1 Predictive marker investigations

This section was changed as a result of Modification 2.

New text:

Prediction Biomarker:

For subjects to be enrolled in study Part 1 / MTD expansion (all comer), and subjects to be enrolled in Study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) and subjects to be enrolled in Study Part 3 MTD expansion (sqNSCLC + LAC + BC) biomarker analysis will be done prior study start (subject stratification) on either a fresh or archival tumor biopsy sample to confirm high fibroblast growth factor receptor (FGFR) expression levels / FGFR mutation (see Section 7.1.1: Inclusion criteria).

Rationale for the quantification of tumor FGFR-1 -2- and -3 levels

…

We therefore consider to stratify sqNSCLC, LAC, BC and SCCHN subjects to be enrolled in study Part 2 and Part 3 / MTD expansion by the quantification of total FGFR mRNA expression levels in archival tissue samples in order to exclude subjects that are unlikely to benefit from BAY1163877 therapy due to low overall FGFR target expression levels.

Rationale for the detection of genetic alterations in FGFR encoding genes and in FGFR pathway downstream signaling molecules

In subjects included in study Part 1 / MTD expansion (all comer), Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) and Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC), genetic testing of tumor tissue may be necessary if a subject lacks a treatment response to BAY 1163877 despite FGFR overexpression in tumor. …. Existence of such FGFR downstream pathway activating mutations in the case of lack of response to BAY 1163877 treatment - despite high total FGFR mRNA tumor expression levels - should be evaluated retrospectively in subjects enrolled in study Part 1 / MTD expansion (all comer), Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN) and Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC).

…

15.6.2.28 Section 9.5.4.2 Laboratory examinations

This section was changed as a result of Modification 2.

New text:

Blood and urine samples for the safety laboratory tests, biomarker investigations, and gene expression profiling and cytokine levels will be collected by a member of the investigator's team.

The laboratory test results will be made promptly available to the investigator except for the biomarker parameters and cytokine levels, which will be analyzed in batches where appropriate.

...

- Gene expression profiling (nCounter PanCancer Immune Profiling Panel)
- Immunhistochemistry for CD8+ T cell infiltration and PD-L1 expression

Peripheral Blood:

- Collection of serum to determine cytokine levels (IL-6, IFN-gamma, and others if needed)

Subjects with BC with low overall FGFR expression levels can only be included in study Part 2 or Part 3 if an activating mutation in FGFR3 gene has been confirmed at screening.

15.6.2.29 Section 10.5 Planned interim analysis

This section was changed as a result of Modification 2.

New text:

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").

15.6.2.30 Section 10.7 Determination of sample size

This section was changed as a result of Modification 2.

Old text

In study Part 2 / MTD expansion, additional subjects will be included in order to obtain further safety and PK data at the MTD level in at least 20 subjects with sqNSCLC or LAC, ~~approximately~~ 30 subjects with BC and at least 8 subjects with SCCHN.

New text:

In study Part 2 / MTD expansion, additional subjects will be included in order to obtain further safety and PK data at the MTD level in at least 20 subjects with sqNSCLC or LAC, at least 30, up to a maximum of 50 evaluable subjects with BC and at least 8 subjects with SCCHN.

In study Part 3 / MTD expansion "Safety cohort", additional subjects will be included to expand the safety database, to collect additional efficacy data, and to assess changes of the immune parameters following treatment at the MTD level in approximately 20 subjects with sqNSCLC or LAC, and approximately 20 subjects with BC.

15.6.2.31 Section 11.1 Data recording

This section was changed as a result of Modification 2.

New text:

…

- Cancer classification including primary diagnosis (all comer for study Part 1; sqNSCLC, LAC, BC or SCCHN for Part 2; sqNSCLC, LAC or BC for Part 3), complete medical / oncological history data and TNM classification

…

15.6.2.32 Section 13.2 Subject information and consent

This section was changed as a result of Modification 2.

New text:

SIS / ICF for FGFR expression / FGFR mutation testing

For subject stratification in the MTD expansion cohorts (Part 1: all comer; Part 2: sqNSCLC + LAC + BC + SCCHN, Part 3: sqNSCLC + LAC + BC), a separate SIS / ICF will be provided to subjects for FGFR expression / FGFR mutation testing.

15.6.2.33 Section 13.3 Publication policy

According to modification 6 of Amendment 5 the name of the sponsor Bayer Health Care AG was renamed to Bayer AG. Section 13.3 was now amended accordingly.

Old text:

All data and results and all intellectual property rights in the data and results derived from the trial will be the property of the Bayer ~~HealthCare~~, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, whilst free to utilize data derived from the trial for scientific purposes, must discuss any publication with Bayer ~~HealthCare~~ prior to release and obtain written consent of Bayer ~~HealthCare~~ on the intended publication. Bayer ~~HealthCare~~ recognizes the right of the investigator to publish the results upon completion of the trial. However, the investigator must send a draft manuscript of the publication or abstract to Bayer ~~HealthCare~~ 30 days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between Bayer ~~HealthCare~~ AG and the investigator(s), the contents of the publication will be discussed in order to find a solution that satisfies all parties.

New text:

All data and results and all intellectual property rights in the data and results derived from the trial will be the property of the Bayer AG, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, whilst free to utilize data derived from the trial for scientific purposes, must discuss any publication with Bayer AG prior to release and obtain written consent of Bayer AG on the intended publication. Bayer AG recognizes the right of the investigator to publish the results upon completion of the trial. However, the investigator must send a draft manuscript of the publication or abstract to Bayer AG 30 days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between Bayer AG and the investigator(s), the contents of the publication will be discussed in order to find a solution that satisfies all parties.

15.6.2.34 Section 14 Reference list

This section was changed as a result of Modification 2.

New reference:

(40) Sweis RF, Spranger S, Bao R, Paner GP, Stadler WM, Steinberg G, Gajewski TF. Molecular Drivers of the Non-T-cell-Inflamed Tumor Microenvironment in Urothelial Bladder Cancer. Cancer Immunol Res. 2016 Jul;4(7):563-8. doi: 10.1158/2326-6066.CIR-15-0274. Epub 2016 May 17.

15.6.2.35 Section 16.1 Study flow chart

This section was changed as a result of Modification 2.

New text:

Table 16-1: Study flow chart: Pre-Treatment – Study Part 1, and Part 2 and Part 3

Measures / actions	FGFR expression / FGFR mutation testing Only for subjects recruited for MTD expansion cohorts (Part 1, Part 2, Part 3)	Screening	
		Within 28 Days* before first study drug administration	Within 7 Days* before first study drug administration
Stratification of subjects to be enrolled in MTD expansion cohorts (Part 1, Part 2 and Part 3)(F)			
Part 3 only: Peripheral blood collection for serum cytokine level (K)			**X**

(E) A pre-treatment biopsy at screening will be obtained from all subjects who agreed on this. For subjects in Part 3 the fresh biopsy for immune response is mandatory. The biopsy sample will be sent to laboratory for biomarker evaluation, see Table 16 5, Table 16 6 and Table 16 7.

(K) For details see Table 16 8

Table 16-3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1, Part 2 and Part 3 (continued)

Measures / actions	TREATMENT											FOLLOW-UP
	Cycle 1 (21 days)					Cycles 2-12 (21 days)			Cycles ≥13 (21 days)		EOT Visit Within 0-14 days after last dose	FU-Visit / Phone Call(A) At 30-35 days after last dose
Day (D)	D1	D2	D3	D8 ±1	D15	D1	D8 ±1	D15 ±1	D1	D11		
Part 3 only: obtain fresh tumor biopsy (G)						X (Between Day 1 to Day 21)						
Part 3 only: peripheral blood collection (N)				X		X^N		X^N				
PK blood sampling (H)	**X→**		**→X**		**X**	**X^H**						

(G) ..
A biopsy in Cycle 2, between Days 1 and 21 inclusively is mandatory …
… for subjects in **Part 3** / MTD expansion (sqNCSLC + LAC + BC)".

(H) PK sampling will be done as follows (for details see Laboratory Manual):•
Cycle 1, Day 1: single-dose PK (all subjects of study Part 1 and at least 12 subjects of study Part 2 and approximately 8 subjects of the MTD expansion cohorts with impaired renal function at baseline

…

Cycle 1, Day 15: multiple-dose PK (all subjects of study Part 1 and 3 and at least 12 subjects of study Part 2 and approximately 8 subjects of the MTD
Cycle 2: Subjects in Part 3/ MTD expansion "Safety cohort" will provide one PK sample within 1 hour of biopsy collection in Cycle 2

(I) All subjects participating in the MTD expansion cohorts (Part 1, Part 2 or Part 3 [not in subjects with impaired renal function]) will have 2 PK samples drawn for the purpose of exposure-response modeling 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). The dose needs to be taken under supervision and the time recorded.

(K) Subjects with PK assessment (all subjects of study Part 1 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 a single-dose of BAY 1163877 on Cycle 1, Day 1 (morning),…

(L) Subjects without PK assessment in study Part 2 and subjects in study Part 3 will receive BAY 1163877 twice daily from Cycle 1, Day 1 ongoing.

(N) Peripheral blood sample for determination of serum cytokine level will be collected at the following timepoints: at baseline; Cycle 1, Day 8; Cycle 2, Day 1; Cycle 2, Day 15; and at day of second biopsy, for details see Table 16-8

15.6.2.36 Section 16.2 Laboratory examinations

This section was changed as a result of Modification 2.

New text:

Table 16-4: Parameters and time points of laboratory examinations performed at local laboratory or study site (safety laboratory) – Study Part 1, Part 2 and Part 3

Table 16-8: Parameters and time points for biomarker investigations in study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC)

Parameters	PRE-TREATMENT		TREATMENT					
	FGFR expression / FGFR mutation testing	Screening	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 2 Day 15
Fresh tumor biopsy		X(A)					X(B)	
Peripheral blood samples (B)		X		X		X(C)		X
Tumor tissue for FGFR expression								
FGFR1/2/3 expression	X(D)							
FGFR and FGFR pathway mutations	X(D)							

(A) An additional biopsy is not requested if a fresh biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit.

(B) A second mandatory tumor biopsy must be obtained between Cycle 2, Day 1 and Cycle 2, Day 21.

(C) Peripheral blood will be collected for determination of serum cytokine levels at the following timepoints: at baseline; Cycle 1, Day 8; Cycle 2, Day 1; Cycle 2, Day 15; and on the day of the second biopsy

(D) An archival or fresh tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels, necessary for subject stratification (see Section 7.1.1: Inclusion criteria). If no archival biopsy sample is available which has been handled and processed as described in the lab manual, collection of fresh tumor biopsy material is mandatory for stratification.
The evaluation of FGFR pathway mutations is planned retrospectively for all subjects.

15.6.2.37 Section 16.3 Listing of instructions and manuals

This section was changed as a result of Modifications 1.

Old text:

~~Sample Handling Procedure Sheet / Manuals~~

Instructions for handling of biologic samples for safety laboratory evaluations and PK assessments are given in ~~the sample handling procedure sheet in the study file and / or~~ Laboratory Manual. These document~~s~~ comprise all relevant measures for the sampling, handling, storage and shipment of the biomatrices (e.g. blood-plasma, urine etc.) ~~including sampling~~. ~~It is provided by the department responsible for bioanalysis.~~

New text:

Instructions for handling of biologic samples for safety laboratory evaluations and PK assessments are given in a separate document (e.g. Laboratory Manual). These document comprises all relevant measures for the sampling, handling, storage and shipment of the biomatrices (e.g. blood-plasma, urine etc.).

15.7 Amendment 9

Amendment no.9 is a global amendment forming integrated protocol version 8.0, dated 17 Oct 2018.

Overall rationale for the amendment

The protocol was amended to allow patients a possibility to continue treatment with rogaratinib and/or follow-up in a roll-over study after the study completion.

Changes to the protocol text

Changes to the protocol text are provided in a separate track-changes version.

High-level description of the changes and the affected sections are listed in the table below.

Section # and Name	Description of Change	Brief Rationale
6.3 End of study, 8.2 Identity of study treatment, 8.8 Post-study therapy, 10.1 General considerations, 12 Premature termination of the study	Protocol was modified to introduce a roll-over study.	A roll-over study was introduced to allow a possibility to continue study treatment and/or follow-up in a separate study when this trial is stopped but benefits are observed for individual patients and/or follow up of patients is needed.

16 Appendices

16.1 Study flow chart - amended

Table 16-1, Table 16-2 and Table 16-3 in the following provide flow charts presenting the time points for the study related measures / actions.

Table 16-1: Study flow chart: Pre-Treatment – Study Part 1, Part 2 and Part 3- amended

Measures / actions	**FGFR expression / FGFR mutation testing** Only for subjects recruited for MTD expansion cohorts (Part 1, Part 2, Part 3)	**Screening** **Within 28 Days***	**Within 7 Days* before first study drug administration**
Signed informed consent	**X**[(A1)]	**X**[(A2)]	
Limited inclusion criteria	**X**		
Inclusion / exclusion criteria		**X**	**X**
Demographic data	**X**[(J)]	**X**[(J)]	
Documentation of the primary diagnosis (refractory, locally advanced or metastatic solid tumor) using the complete pathological report	**X**[(J)]	**X**[(J)]	
Complete medical / oncological history	**X**[(J)]	**X**[(J)]	
TNM classification	**X**[(J)]	**X**[(J)]	
Concomitant diseases, NYHA grading		**X**	
Review of baseline toxicities	**(X)**	**X**	**X**
Baseline characteristics (smoking habits / history, alcohol consumption)		**X**	
Previous therapy		**X**	
Concomitant therapy		**X**	**X**
Physical examination		**X**	
Body height			**X**
Body weight / calculation of BMI[(B)]			**X**
Vital signs[(C)]			**X**
ECOG performance status	**X**	**X**	
12-lead ECG[(D)]		**X**	
Obtain pre-treatment biopsy[(E)]		**X**	
Obtain archival tissue sample or fresh tumor material for FGFR expression / FGFR mutation testing	**X**		

Continued

Table 16-1: Study flow chart: Pre-Treatment – Study Part 1, Part 2 and Part 3 - amended[91]

Measures / actions	**FGFR expression / FGFR mutation testing** Only for subjects recruited for MTD expansion cohorts (Part 1, Part 2 and Part 3)	**Screening**	
		Within 28 Days*	**Within 7 Days* before first study drug administration**
Stratification of subjects to be enrolled in MTD expansion cohorts (Part 1, Part 2 and Part 3)(F)	**X**		
Blood / urine collection for safety lab tests(G)		**X**	**X**
Part 3 only: Peripheral blood collection for serum cytokine level(K)			**X**
Only females: Urine pregnancy test			**X**
Calculation of eGFR(H)			**X**
Ophthalmological examination at consultant		**X**	
CT / MRI scans		**X**	
Documentation of lesion(s) according to RECIST v1.1			**X**
Adverse events(I)	**(X)**	**X**	**X**

*Pre-study examinations may require hospitalization for 1- 2 days.

(A1) Informed consent for FGFR expression / FGFR mutation testing

(A2) Informed consent for study treatment eligibility can be signed before 28-day screening phase.

(B) BMI (body mass index) is calculated by dividing the subject's weight by the square of his / her height (kg/cm^2).

(C) Vital signs (body temperature, respiration, systolic / diastolic blood pressure, heart rate); for methods of measurement, see Section 9.4.1.1 (Cardiovascular assessment) and Section9.5.3.3 (Vital signs).

(D) At screening, single ECG readings (in the supine position) should be performed.

(E) A pre-treatment biopsy at screening will be obtained from all subjects who agreed on this. For subjects in Part 3 the fresh biopsy is mandatory. The biopsy sample will be sent to laboratory for biomarker evaluation, see Table 16-5, Table 16-6 and Table 16-7.

91 Table 16-1 was modified by Amendment 7, see section 15.6.2.35

Table 16-1: Study flow chart: Pre-Treatment – Study Part 1, Part 2 and Part 3 (Continued)

((F)	For details, see Table 16-6 and Table 16-7
(G)	Safety lab tests: Virology tests within 28 days before first study drug administration, all other blood and urine tests within 7 days before first study drug administration, for details see Table 16-4. H) For calculation of eGFR (estimated glomerular filtration rate), see Section 16.9.
(I)	Signs and symptoms that existed prior to signing informed consent should be recorded as medical history findings. Signs and symptoms worsened after the informed consent was signed as well as any sign or symptom that begins after the informed consent was signed (even if prior to start of study medication) should be recorded on an adverse event page of the eCRF using CTCAE v4.03. AE does only to be recorded for period of FGFR expression / FGFR mutation testing in pre-treatment in case an invasive procedure was performed to obtain tumor material.
(J)	Documentation has not to be provided twice for subjects enrolled in the MTD expansion cohorts.
(K)	For details see Table 16-8

Table 16-2: Study flow chart: Treatment (Cycle 1, Day -3 to Day -1) – Study Part 1 and Part 2

Measures / actions	**TREATMENT (only for "tablet bridging cohort" (Part 1) and for "food effect assessment" (Part 1 and Part 2))**		
	Cycle 1		
	Day -3	Day -2	Day -1
Concomitant medication	**X**	**X**	**X**
Physical examination	**X**	**X**	**X**
Ask subject for changes in vision(A)	**X**	**X**	**X**
Cardiovascular assessment(B)	**X→ → X**		**X**
Body temperature	**X**	**X**	**X**
Body weight	**X**		
12-lead ECG readings(C)	**X**	**X**	
ECOG performance status	**X**	**X**	**X**
Blood / urine collection for safety lab tests(D)	**X**		
Calculation of eGFR(E)	**X**		
PK blood sampling(F)	**X→ → X**		
Administration of BAY 1163877 (single dose) after a high-fat, high-calorie breakfast(G)	**X**		
Administration of BAY 1163877 tablet (single dose)(H)	**X**		
Toxicities / AE assessment	**X**	**X**	**X**

(A) If change in vision is reported by subject an ophthalmological examination must be performed (see Section 9.5.3.2)

(B) Cardiovascular assessment: Blood pressure (BP) and heart rate (HR) will be measured as follows (see Section 9.4.1.1): before and 0.5, 1, 2, 3, 4, 6, 8, 12 (Day -3), 24 (Day -2) and 48 (Day -1) hour(s) after single-dose administration.

If a reduction of systolic BP below 90 mmHg or an increase in HR to more than 120 bpm is detected, the assessment has to be repeated after 2 hours. When blood pressure measurement and PK sample collection are scheduled at the same time point, subject's blood pressure will be measured before collection of the PK sample.

(C) 12-lead ECGs should be performed in triplicate in close sequence and **not more than 2 minutes apart**. ECG readings will be performed at the following time points: before and 2, 3 (Day -3) and 24 (Day -2) hours after single-dose administration.

(D) Safety laboratory tests, see Table 16-4

(E) For calculation of eGFR (estimated glomerular filtration rate), see Section 16.9

(F) PK sampling will be done as follows (for details see separate document e.g. Laboratory Manual):

- pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12 (Day -3), 24 (Day -2) and 48 (Day -1) hour(s) after single-dose administration

Continued

Table 16-2: Study flow chart: Treatment (Cycle 1, Day -3 to Day -1 – Study Part 1 and Part 2 (Continued)

(G)	*Only for subjects with "food effect assessment" in Part 1 and Part 2*: Oral administration of a single dose of BAY 1163877 immediately (within 5 minutes) after consumption of a high-fat, high-calorie breakfast (supervised by a member of the site), see Section 8.4.2.2.1.
(H)	*Only for subjects included in the "tablet bridging cohort" of Part 1 / dose escalation:* Oral administration of BAY 1163877 tablet formulation on Cycle 1, Day -3 will be done by a member of the site.

Table 16-3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1, Part 2 and Part 3 (continued) - amended

Measures / actions	TREATMENT											FOLLOW-UP
	Cycle 1 (21 days)					Cycles 2-12 (21 days)			Cycles ≥13 (21 days)		EOT Visit Within 0-14 days after last dose	FU-Visit / Phone Call[A] At 30-35 days after last dose
Day (D)	D1	D2	D3	D8 ±1	D15	D1	D8 ±1	D15 ±1	D1	D11		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X
Ask subject for changes in vision[B]	X	X	X	X	X	X	X	X	X	X	X	X
Cardiovascular assessment[C]	X→ → X		X	X	X	X	X	X	X	X	X	X
Body temperature	X	X	X	X	X	X			X		X	
Body weight	X					X			X		X	
12-lead ECG readings[D]	X	X			X	X			X		X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	
Blood / urine collection for safety lab tests[E]	X			X	X	X	X	X	X	X	X	
Calculation of eGFR[F]	X			X	X	X	X	X	X	X	X	
24-hour urine collection[M]	X											
Obtain tumor biopsy for biomarker tests[G]						X (Cy 2 only)						
Part 3 only: obtain fresh tumor biopsy [G]						X (Between Day 1 to Day 21)						
Part 3 only: peripheral blood collection [N]				X		X^N		X				
PK blood sampling[H]	X→ → X				X	X^H						
PK blood sampling for PK / PD modeling[I]						X						
Ophthalmological examination						Every 2nd cycle					X	
CT / MRI scans and documentation of response according to RECIST v1.1						End of Cycle 2, then after every 3rd cycle						

Table 16-3: Study flow chart: Treatment (Cycle ≥ 1) and Follow-up – Study Part 1, Part 2 and Part 3 (Continued) - amended

Measures / actions	TREATMENT											FOLLOW-UP
	Cycle 1 (21 days)					Cycles 2-12 (21 days)			Cycles ≥13 (21 days)		EOT Visit Within 0-14 days after last dose	FU-Visit / Phone Call(A) At 30-35 days after last dose
Day (D)	D1	D2	D3	D8 ±1	D15	D1	D8 ±1	D15 ±1	D1	D11		
Dispense / return of BAY 1163877 and diary(J)	X		X	X	X	X	X	X	X	X	X	
Administration of BAY 1163877 if PK assessment (K)	X		Continuous, twice-daily administration									
Administration of BAY 1163877 if no PK assessment(L)	Continuous, twice-daily administration											
Toxicities / AE assessment	X	X	X	X	X	X	X	X	X	X	X	X

A time window of ±1 day is allowed on visits with no PK sampling.

(A) FU-Visit will be performed for subjects who have not started a new treatment. For subjects who have started a new antitumor treatment, only a phone call will be made.

(B) If change in vision is reported by subject an ophthalmological examination (see Section 9.5.3.2) must be performed

(C) Cardiovascular assessment: Blood pressure (BP) and heart rate (HR) will be measured as follows (see Section 9.4.1.1):

- Cycle 1, Day 1 and Day 2: before and 0.5, 1, 2, 3, 4, 6, 8, 12 (Day 1), and 24 (Day 2) hour(s) after single-dose administration
- Cycle 1, Day 3: before and 1 and 2 hour(s) after morning dose
- Cycle 1, Day 8: (one measurement)
- Cycle 1, Day 15: before and 0.5, 1, 2, 3, 4, 6, 8 and 12 hour(s) after morning dose (12-hour measurement before evening dose)
- Cycle ≥ 2: each visit (one measurement)
  - Follow up : EOT visit (one measurement) and FU-visit (one measurement)

If a reduction of systolic BP below 90 mmHg or an increase in HR to more than 120 bpm is detected, the assessment has to be repeated after 2 hours. When blood pressure measurement and PK sample collection are scheduled at the same time point, subject's blood pressure will be measured before collection of the PK sample.

Continued

Table 16-3: Study flow chart: Treatment (Cycle ≥1) and Follow-up – Study Part 1, Part 2 and Part 3 (Continued) - amended

(D) In Cycle 1, all 12-lead ECGs should be performed at the following time points:

Cycle 1, Day 1 and Day 2 (single ECG reading): before and 2, 3 (Day 1) and 24 (Day 2) hours after single-dose administration
Cycle 1, Day 15 (single ECG reading): before morning dose, and 2 and 3 hours thereafter
Cycle ≥ 2, Day 1 (single ECG reading): after morning dose
EOT visit (single ECG reading)

(E) Safety laboratory tests, see Table 16-4

(F) For calculation of eGFR (estimated glomerular filtration rate), see Section 16.9

(G) A tumor biopsy on Cycle 2, Day 1 will be obtained from all subjects who agreed on this at screening. The biopsy sample will be send to laboratory for biomarker evaluation, see Table 16-5, Table 16-6 and Table 16-7.

A biopsy on Cycle 2, Day 1 is optional …
…for subjects in study Part 1 / dose-escalation (all comer).
…for subjects in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN).

A biopsy on Cycle 2, Day 1 is mandatory …
…for subjects in study Part 1 / MTD expansion (all comer).
A biopsy in Cycle 2, between Days 1 and 21 inclusively is mandatory …
… for subjects in **Part 3** / MTD expansion (sqNCSLC + LAC + BC)"

(H) PK sampling will be done as follows (for details see Laboratory Manual):•

- Cycle 1, Day 1: single-dose PK (all subjects of study Part 1 and at least 12 subjects of study Part 2 and approximately 8 subjects of the MTD expansion cohorts with impaired renal function at baseline)
  - pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hour(s) after single-dose administration (48-hours sample before morning dose on Day 3)
- Cycle 1, Day 15: multiple-dose PK (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)

before and 0.5, 1, 2, 3, 4, 6, 8 and 12 hour(s) after morning dose on Cycle 1, Day 15 (12-hour sample before administration of evening dose)
Cycle 2: Subjects in Part 3/ "Safety cohort" will provide one PK sample within 1 hour of biopsy collection in Cycle 2

(I) All subjects participating in the MTD expansion cohorts (Part 1, Part 2 or Part 3 [not in subjects with impaired renal function]) will have 2 PK samples drawn for the purpose of exposure-response modeling 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). The dose needs to be taken under supervision and the time recorded.

Table 16-3: Study flow chart: Treatment (Cycle ≥1) and Follow-up – Study Part 1, Part 2 and Part 3 (Continued)

(J)	First oral administration of BAY 1163877 on Cycle 1 Day 1 will be done with a member of the site. To have complete control over the distribution and use of the study medication, the drug accountability must be performed before new medication is handed out to the subject. Return of BAY 1163877and diary at EOT visit.
(K)	Subjects with PK assessment (all subjects of study Part 1 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 a single-dose of BAY 1163877 on Cycle 1, Day 1 (morning), followed by a "drug-free day" (to enable single dose PK assessments). Subjects with "food effect assessment" in Part 1 and Part 2 take the morning dose after an overnight fast of at least 8 hours (see Section 8.4.2.2.1). 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 each Cycle.
(L)	Subjects without PK assessment in study Part 2 and subjects in study Part 3 will receive BAY 1163877 twice daily from Cycle 1, Day 1 ongoing.
(M)	In approximately 8 subjects enrolled in MTD expansion cohorts (study Part 1 and Part 2), urine will be collected for 24 hours after dosing.
(N)	Peripheral blood sample for determination of serum cytokine level will be collected at the following timepoints: at baseline; Cycle 1, Day 8; Cycle 2, Day 1; Cycle 2, Day 15; and at day of second biopsy, for details see Table 16-8

[92]

[92] Table 16-3 was modified by Amendment 7, see section 15.6.2.35

16.2 Laboratory examinations - amended

Table 16-4, Table 16-5, Table 16-6, Table 16-7 and Table 16-8 provide the parameters and time points for the laboratory examinations (safety laboratory tests, biomarker investigations, cytokines) to be performed during the study. Instructions for biomarker and PK sample collection, processing, storage and shipment will be described in a separate document (e.g. lab manual).

Table 16-4: Parameters and time points of laboratory examinations performed at local laboratory or study site (safety laboratory) – Study Part 1, Part 2 and Part 3 - amended [93]

Parameters	PRE-TREATMENT		TREATMENT						FOLLOW-UP	
	FGFR expression / FGFR mutation testing	Screening	Cycle 1	Cycles 1-12			Cycle ≥13		EOT visit	FU visit
			Day -3	Day 1	Day 8	Day 15	Day 1	Day 11		
BLOOD										
Hematology: Erythrocytes (RBC), hemoglobin, hematocrit, platelet count, MCV, MCH, MCHC, leucocytes (WBC), including differential WBC (absolute count of neutrophils, lymphocytes, monocytes, basophils, and eosinophils)		X	X	X	X	X	X	X	X	
Coagulation: PT or PT-INR (obligatory at screening) and PTT (aPTT)[(A)]		X		X			X		X	
Biochemistry: AST / GOT, ALT / GPT, gamma-GT, AP, LDH, amylase, lipase, glucose, triglycerides, creatinine[(B)], BUN, uric acid, bilirubin (total & direct), total protein, albumin, sodium, potassium, chloride, CPK, calcium, phosphate		X	X	X	X	X	X	X	X	
Virology: HBs-Ag, anti-HCV, anti-HIV 1+2		X								
URINE										
Macroanalysis: Clarity of urine: clear, slightly clear, cloudy, or turbid		X	X	X	X	X	X	X	X	
Urinalysis (dip stick): pH, blood, protein, glucose, bilirubin, urobilinogen, ketone, nitrite, leucocytes (or leucocyte esterase), specific gravity		X	X	X	X	X	X	X	X	
Laboratory analysis[(C)]: Protein and creatinine		X	X	X	X	X	X	X	X	
Microscopic urinalysis[(D)]: Erythrocytes, leucocytes, epithelia cells, bacteria crystals, casts, bacteria and yeast		X	X	X	X	X	X	X	X	
Pregnancy test[(F)]		X								

93 Part 3 added by Amendment 7

Table 16-4: Parameters and time points of laboratory examinations performed at local laboratory or study site (safety laboratory) – Study Part 1, Part 2 and Part 3

(A)	For all subjects
(B)	The serum creatinine concentration is used to estimate the subject's glomerular filtration rate (see Section **16.9**)
(C)	Random urine sample preferably taken at mid-morning for the quantification of proteinuria by urinary protein/creatinine ratio
(D)	Only if urine appearance is turbid, or if protein, leukocytes, erythrocytes, or nitrite are out of normal range)
(F)	Only females of childbearing potential

Table 16-5: Parameters and time points for biomarker investigations in study Part 1 / dose escalation (all comer)

Parameters	PRE-TREATMENT		TREATMENT									FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycle 1 Day 1	Day 3	Day 8	Day 15	Cycles 2-12 Day 1	Day 8	Day 15	Cycles ≥13 Day 1	Day 11	EOT visit
Tumor tissue: p-ERK1/2 levels		X(A)					X(B) only Cycle 2					
Blood (serum) samples*:												
FGF23		X	X	X	X	X	X	X	X	X	X	X
Phosphate, Calcium		X	X	X	X	X	X	X	X	X	X	X

p-ERK = phospho-extracellular signal–regulated kinase
FGF23 = fibroblast growth factor 23

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877 only for Cycle 1.

(A) A pre-treatment biopsy (e.g. endoscopic or ultrasound-guided biopsy) will be obtained at screening if the subject agreed on this (optional biopsy). Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

(B) A second biopsy may be taken on Cycle 2, Day 1 if the subject agreed on this at screening (optional biopsy).

p-ERK1/2 levels will only be analyzed if a subject is willing to undergo both a pre-treatment biopsy at screening and a second biopsy on Cycle 2, Day 1.

Table 16-6: Parameters and time points for biomarker investigations in study Part 1 / MTD expansion (all comer)

Parameters	PRE-TREATMENT		TREATMENT					FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycles 1-12 Day 1	Day 8	Day 15	Cycles ≥13 Day 1	Day 11	EOT visit
Tumor tissue:								
p-ERK1/2 levels		X(A)	X(B) only Cycle 2					
FGFR1/2/3 expression	X(C)							
FGFR and FGFR pathway mutations	X(C)							
Blood (serum) samples*:								
FGF23		X	X	X	X	X	X	X
Phosphate, Calcium		X	X	X	X	X	X	X

p-ERK = phospho-extracellular signal–regulated kinase
FGFR 1/2/3 = fibroblast growth factor receptor 1, 2 and 3
FGF23 = fibroblast growth factor 23

* Blood (serum) samples to be collected before administration of the morning dose of BAY 1163877 only for Cycle 1.

(A) An additional biopsy is not requested if a biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit. Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

(B) A second mandatory tumor biopsy must be obtained on Cycle 2, Day 1.

(C) An archival or fresh tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels, necessary for subject stratification (see Section 7.1.1: Inclusion criteria). If no archival biopsy sample is available which has been handled and processed as described in the lab manual, collection of fresh tumor biopsy material is mandatory for stratification.
The evaluation of FGFR pathway mutations is planned retrospectively for all subjects.

Table 16-7: Parameters and time points for biomarker investigations in study Part 2 / MTD expansion (sqNSCLC + LAC + BC + SCCHN)

Parameters	PRE-TREATMENT		TREATMENT					FOLLOW-UP
	FGFR expression / FGFR mutation testing	Screening	Cycles 1-12			Cycles ≥13		EOT visit
			Day 1	Day 8	Day 15	Day 1	Day 11	
Tumor tissue:								
p-ERK1/2 levels		X(A)	X(B) only Cycle 2					
FGFR1/2/3 expression	X(C)							
FGFR and FGFR pathway mutations	X(C)							

p-ERK = phospho-extracellular signal–regulated kinase
FGFR 1/2/3 = fibroblast growth factor receptor 1, 2 and 3

(A) A pre-treatment biopsy (e.g. endoscopic or ultrasound-guided biopsy) will be obtained at screening if the subject agreed on this. The pre-treatment biopsy is optional for subjects for whom an archival biopsy is available. An additional biopsy is not requested if a biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit.
Anticancer chemotherapy must have been stopped for at least 5 half-lives of the last applied therapy before the pre-treatment biopsy is taken. Mitomycin C, nitrosoureas or monoclonal antibodies with anticancer activity (e.g. bevacizumab or cetuximab etc.) should not be given within 6 weeks of pre-treatment biopsy for biomarker (p-ERK1/2) studies.

(B) A second biopsy will be taken on Cycle 2, Day 1 if the subject agreed on this at screening (optional biopsy).

(C) An archival tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels necessary for subject stratification (see Section 7.1.1: Inclusion criteria). If no archival biopsy is available which has been handled and processed as described in the lab manual, collection of fresh tumor biopsy material is mandatory for stratification.
Samples of BC subjects will also be tested on activating FGFR3 mutation status for stratification.
The evaluation of FGFR pathway mutations is planned retrospectively for all subjects.

p-ERK1/2 levels will only be analyzed if a subject is willing to undergo both a pre-treatment biopsy at screening and a second biopsy on Cycle 2, Day 1.

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Table 16-8: Parameters and time points for biomarker investigations in study Part 3 / MTD expansion "Safety cohort" (sqNSCLC + LAC + BC)

Parameters	PRE-TREATMENT		TREATMENT					
	FGFR expression / FGFR mutation testing	Screening	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 2 Day 15
Fresh tumor biopsy		X(A)					X(B)	
Peripheral blood samples (B)		X		X		X(C)		X
Tumor tissue for FGFR expression								
FGFR1/2/3 expression	X(D)							
FGFR and FGFR pathway mutations	X(D)							

(A) An additional biopsy is not requested if a fresh biopsy was already obtained for FGFR expression / FGFR mutation testing prior to the screening visit.

(B) A second mandatory tumor biopsy must be obtained between Cycle 2, Day 1 and Cycle 2, Day 21.

(C) Peripheral blood will be collected for determination of serum cytokine levels at the following timepoints: at baseline; Cycle 1, Day 8; Cycle 2, Day 1; Cycle 2, Day 15; and on the day of the second biopsy

(D) An archival or fresh tumor tissue specimen will be used for the quantification of fibroblast FGFR expression levels, necessary for subject stratification (see Section 7.1.1: Inclusion criteria). If no archival biopsy sample is available which has been handled and processed as described in the lab manual, collection of fresh tumor biopsy material is mandatory for stratification.
The evaluation of FGFR pathway mutations is planned retrospectively for all subjects.

94 Table 16-8 was added by Amendment 7, see section 15.6.2.36

16.3 Listing of instructions and manuals - amended

Instructions for handling of biologic samples for safety laboratory evaluations and PK assessments are given in a separate document (e.g. Laboratory Manual). This document comprises all relevant measures for the sampling, handling, storage and shipment of the biomatrices (e.g. blood-plasma, urine etc.). [95]

[95] This section was amended for clarification by Amendment 7

16.4 Model-based dose-response analysis of the DLT rates

16.4.1 Statistical model

The analysis is based on a method reported by Tibaldi et al (2008) (37).

A range of daily doses will be tested, including possibly 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 and 1100mg. 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:

$$\log\left(\frac{p}{1-p}\right) = \alpha + \beta d \, .$$

The prior distribution on α and β determine the prior distribution on the probability of DLT as a function of dose. Prior distributions were elicited. All of the following distributions are independent. The following prior distributions are used in the trial:

$$\alpha \sim \mathrm{N}(\mu = -3, \mathrm{sd} = 1) \, ,$$

and

$$\beta \sim \mathrm{N}_{+}(\mu = 0.0015, \ \mathrm{sd} = 0.003) \, .$$

Based on these distributions, 100 dose-DLT curves from the prior distribution were simulated (see Figure 16-1).

The prior probability distribution for the MTD is summarized in Table 16-9.

Figure 16-1:100 random observations (curves) from the prior distribution

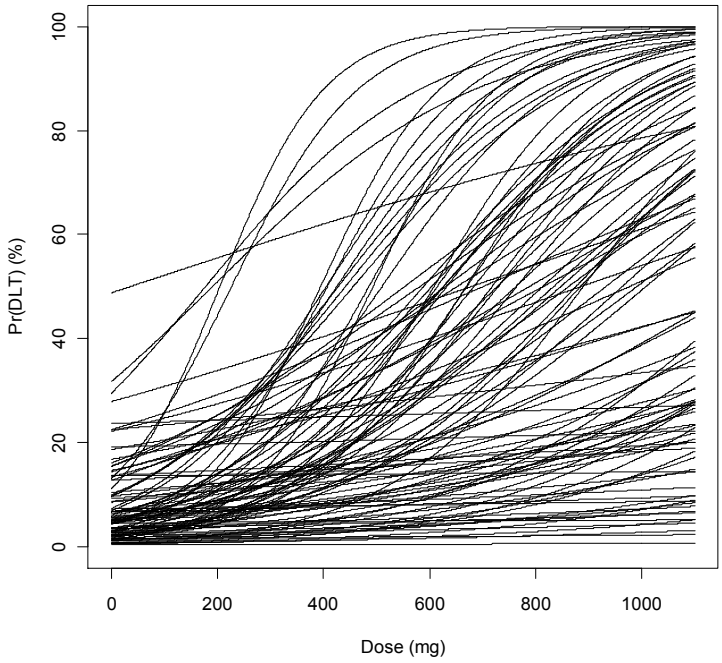


Table 16-9: Prior probability distribution of MTD

MTD range	Prior probability
≤100mg	10.8%
Between 100 and 300mg	17.4%
Between 300 and 600mg	25.0%
Between 600 and 1100mg	19.7%
> 1100mg	27.1%

Given any set of data, the prior distribution can be updated, yielding a posterior distribution of the parameters. From this posterior distribution many different quantities of relevance can be calculated:

- E(p|d) = Posterior mean probability of DLT for dose d.
- 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

- MTD: the dose at which the predicted DLT rate is 20%: $MTD = \frac{\log(0.2/0.8) - \alpha}{\beta}$

Note that, in this model, the MTD is a parameter. It has a probability distribution. A consequence of the Bayesian modeling is the probability, *Q*d, which is the probability that a dose is the MTD. This is a powerful question that cannot be answered from a frequentist perspective.

16.4.2 Trial simulation details

The trial design for purposes of simulation is as follows:

1. Three subjects are assigned to d = 1 (100mg)
2. Pursue the following dose escalation process up to when first DLT is observed:

a. 2-fold dose escalation testing doses up to 1100 mg in cohorts of 3 subjects.

3. If at least one DLT is reported, fit Bayesian model and select next dose as the dose d at which Qd is maximum, or the maximum allowed dose if any of the following constraints are met:

   If 2 DLTs in a cohort of size 3, d must be lower than or equal to that dose.

   If 3 DLTs out of 3 or at least 4 DLTs out of 6, d must be lower than that dose.

   Dose d must be at most 2-fold larger than the maximum dose tested.

Repeat 3, again assigning 3 subjects / cohort to this dose. Terminate study when any of the following stopping rules happen:

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 TN > 80%
3. Minimum dose tested (100mg) is toxic (TN < 20%)
4. Total sample size for next dose is already equal to 9.

16.4.3 Simulation scenarios

Five dose-DLT profiles were considered in order to evaluate the operational characteristics of that adaptive dose escalation trial. The 5 scenarios are:

Scenario A – Maximum dose safe: This scenario represents a negative scenario under which all doses are safe and the true MTD is larger than the maximum possible dose (MTD=10,000 mg).

Scenario B - Late MTD: This is a scenario is which the MTD is 500 mg. The probability of a DLT is gradually increasing across all dose levels.

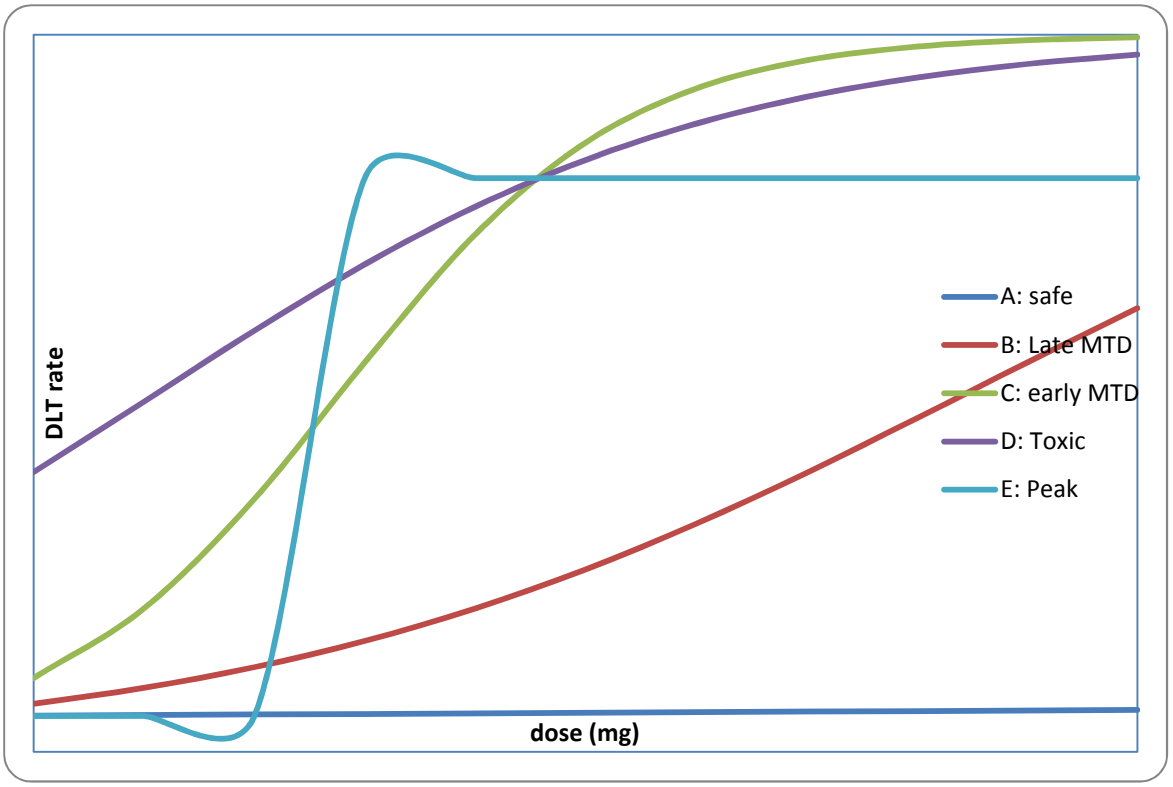
Scenario C – Early MTD: In this scenario, the rate of DLT progression is faster over doses

so that the MTD appears sooner (200 mg).

Scenario D - Toxic: Under this scenario, all doses are toxic, with a DLT rate of 39% at the lowest dose and increasing to 100% at the highest dose level.

Scenario E - Peak: In this scenario there is a step function in the probability of DLT's occurring very early in the dose escalation process. The first doses up to 300 mg are very safe (p=5%), and all subsequent doses are toxic (p=80%).

Figure 16-2:Dose versus DLT rates simulation scenarios



16.4.4 Operational characteristics

We used 1000 trial simulations in order to monitor the following properties of the adaptive design under the 5 scenarios:

- Accuracy and precision of the MTD
- Probability of archiving each of the 3 stopping rules (MTD precision, last dose is safe, max. sample size).
- Total sample size
- Number and proportion of subjects being under-dosed and over-dosed (i.e., relative to

the true MTD)

- Patient distribution across dose levels

16.4.5 Simulation results

Scenario A – Maximum dose safe:

When all doses are safe, the study has 87.4% probability to report a mean MTD larger than 1100mg. It has 75.3% probability to conclude that the maximum dose has a DLT rate of below 20% with 80% confidence. The expected mean ± standard deviation (±sd) sample size is 20.3±2.0 patients in 6.8±0.7 cohorts.

The predicted patient distribution by dose is reported in Figure 16-3 for all 5 scenarii. Under scenario A, as expected, the maximum dose escalation scheme of a 2-fold increase is performed for most simulations. The top dose (1100mg) is, on average (±sd), administered to 8.1±1.7 patients.

Scenario B – Late MTD:

When the true MTD is 500mg, the mean relative bias in the MTD estimate was 26.3%. The study has 81.9% chances to yield a CV (MTD) < 40%. It reaches the cap of N=9 subjects per dose in another 17.9%. At study end, the mean CV of the MTD is 40.1%. The expected mean (±sd) sample size is 18.1±4.4 patients in 6.0±1.5 cohorts. The expected mean (±sd) number of subjects being over-dosed (i.e., at doses larger than 500 mg) is 5.5±3.3.

As shown in Figure 16-3, dose escalation progresses up to 400 mg in a similar way as for scenario 1 with fewer patients being overdosed at 800 mg or 1100 mg and additional subjects receiving a dose of 300 mg.

Scenario C – Early MTD:

When the true MTD is 200mg, the mean relative bias in the MTD estimate was 35.5%. The study has 27.8% chances to yield a CV (MTD) <40% and it reaches the cap of N=9 subjects per dose in another 70.9%. At study end, the mean CV of the MTD is 50.0%. The expected mean (±sd) sample size is 19.6±6.5 patients in 6.5±2.2 cohorts. The expected mean (±sd) number of subjects being over-dosed (i.e., at doses larger than 200mg) is 7.7±6.0.

As shown in Figure 16-3, under scenario C, maximum dose escalation progresses as expected up to 400mg. Then adaptation occurs around the MTD between doses from 100 to 300mg with a peak at 200mg (N=6.2±2.7).

Scenario D – Toxic:

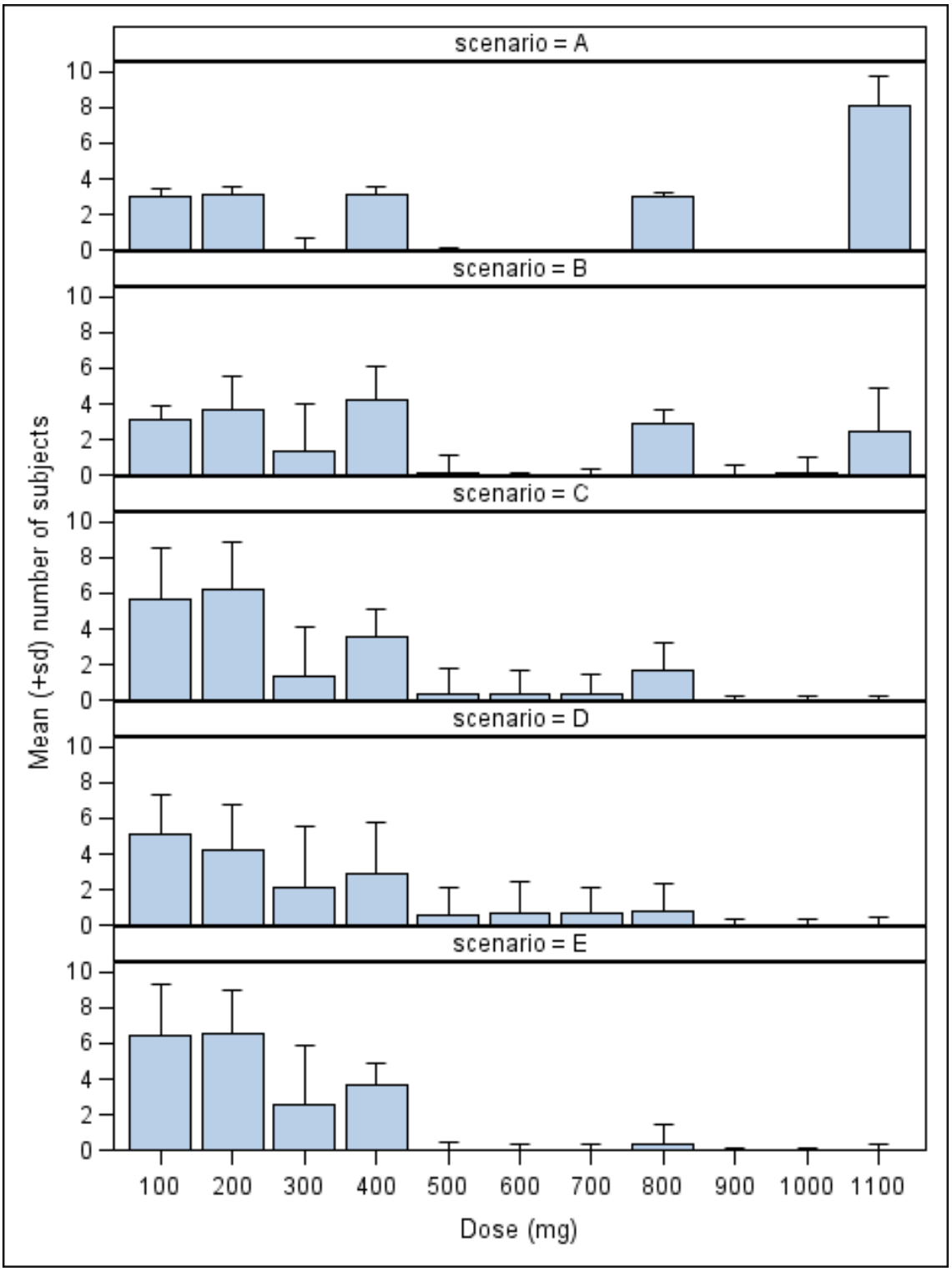
When the DLT rate ranges from 39 to 100%, the study has 57.9% chances to declare that the DLT rate at the lowest dose (100mg) is at least 20% with 80% probability. In another 40.9%, the study will stop when the cap of N=9 subjects per dose is reached. The expected mean (±sd) sample size is 17.0±9.7 patients in 5.7±3.2 cohorts.

As shown in Figure 16-3, under scenario D, the majority of patients receive doses up to 400mg where the predicted DLT rate is 68.0%.

Scenario E – Peak:

When doses up to and including 300 mg are very safe but larger doses are very toxic, the first doses up to 400mg are administered in most patients, as expected. Then adaptation occurs in the 200 -300mg interval. The expected mean (±sd) total sample size is 19.7±4.5 patients in 6.5±1.5 cohorts. The expected mean (±sd) number of subjects being over-dosed (i.e., at doses larger than 300mg) is 4.1± 2.4. Most of these over-dosed patients receive a maximum dose of 400 mg.

Figure 16-3:Predicted mean + sd number of patients per dose by scenario



16.5 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE v4.03)

This study will utilize the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (CTCAE v4.03: June 14, 2010), for toxicity / adverse event and serious adverse event reporting.

All appropriate treatment areas should have access to a copy of the CTCAE v4.03.

A copy of CTCAE v4.03 can be downloaded from

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

(copy link into browser)

16.6 Tumor node metastases (TNM) classification

The International Union Against Cancer (UICC), Tumor Node Metastasis (TNM) Classification of Malignant Tumors (7th edition) will utilized for grading and staging of tumors.

All appropriate treatment areas should have access to a copy of the UICC-TNM v 7.

UICC - TNM Classification of Malignant Tumours

Author(s):

L. H. Sobin, MD, M. K. Gospodarowicz, MD, Prof. Dr. med. Ch. Wittekind

Publisher:

Wiley-Blackwell - A John Wiley & Sons, Ltd., Publication, December 2009

ISBN: 978-1-4443-3241-4

Also available as online version (TNM online)

http://www.wileyanduicc.com/

(copy link into browser)

16.7 Eastern Cooperative Oncology Group (ECOG) performance status

These scales and criteria are used to assess how a subject's disease is progressing and how the disease affects the daily living abilities of the subject.

Table 16-10: ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)
5	Dead

ECOG Performance based on Oken et al. (1982) in Am. J. Clin. Oncol. (36).

16.8 Response evaluation criteria in solid tumors (RECIST v1.1) - amended

Response and progression will be evaluated in this trial using the new international criteria proposed by the RECIST committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria for determination of tumor response. Additionally, per the RECIST working group, CT scan (with contrast) is currently the best available and reproducible method to measure lesions selected for response assessment.

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness ≤ 5 mm)
- 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest x-ray.
- Malignant lymph node: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. Lymph nodes < 10 mm are non-pathological. Lymph nodes measuring ≥10 mm to < 15 mm are considered non-target.

Non-measurable disease: Non-measurable disease is defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm in short axis) as well as truly non-measurable lesions. Lesions considered to be truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of the skin or lung, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations

Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT scan or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurable disease. Blastic bone lesions are considered non-measurable disease. Note: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these can be used to confirm the presence or disappearance of bone lesions.

Cystic lesions: Lesions that meet the criteria to be radiographically defined as simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurable

disease. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Measurement of lesions: All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Target lesions: When more than one measurable lesion is present at baseline, all measurable lesions, up to a maximum of five lesions total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and be recorded and measured at baseline. This means that, in instances where subjects have only one or two organ sites involved, a maximum of two or four lesions, respectively, will be recorded. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those that lend themselves to reproducible repeated measurements. In situations in which the largest lesion does not lend itself to reproducible measurement, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes as target lesions: Pathological nodes, which are defined as measurable and may be identified as target lesions, must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as reference to further characterize the objective tumor response in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required but these lesions should be noted at baseline and should be followed as “present”, “absent”, or in rare cases, “unequivocal progression”. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Best response

All subjects will have their **best response** on trial classified as outlined below and summarized in Table 16-11, Table 16-12 and Table 16-13.

Evaluation of response in target lesions

- **Complete response (CR):** disappearance of all target lesions (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to
  < 10 mm.
- **Partial response (PR):** at least a 30% decrease in the sum of diameters of target lesions taking as the reference the baseline sum of diameters.
- **Stable disease (SD):** steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference, the smallest sum of diameters while in the trial.
- **Progressive disease (PD):** at least a 20% increase in the sum of diameters of the target lesions, taking as a references the smallest sum on study (this includes the baseline sum if that is the smallest on trial). In addition to a relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Appearance of new lesions will also constitute PD.

Special notes on assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero, even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions

Target lesions that become too small to measure

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

Evaluation of response in non-target lesions

Complete response: Disappearance of all non-target lesions and normalization of

tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR / Non-PR: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease: Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression.)

Disease progression in subjects with only non-measurable disease

For subjects with only non-measurable disease, disease progression is defined as development of new lesions or "unequivocal progression" of existing lesions. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden, based on the change in non-measurable disease, is comparable in magnitude to the increase that would be required to declare PD for measurable disease, i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

New lesions

The appearance of new malignant lesions denotes disease progression; however, the finding of a new lesion should be unequivocal, i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions).

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. If a new lesion is equivocal (e.g., because of small size), continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Table 16-11: Target and non-target lesion response - amended

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
CR	CR	No	CR	not earlier than 4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	not earlier than 4 weeks confirmation
CR	Not evaluated	No	PR	not earlier than 4 weeks confirmation
PR	Non-PD or not all evaluated	No	PR	not earlier than 4 weeks confirmation
SD	Non-PD or not all evaluated	No	SD	Documented at least once > 6 weeks from baseline
PD	Any	Yes or No	PD	—
Any	PD	Yes or No	PD	—
Any	Any	Yes	PD	—
Not all evaluated	Non-PD	No	Unevaluable	—

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease;

Subjects with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 16-12: Time-point response: Subjects with non-target disease only - amended

Non-Target Lesions	New Lesions	Overall Response	Best Response also Requires
CR	No	CR	not earlier than 4 weeks confirmation
Non-CR / Non-PD	No	Non-CR /Non-PD[a]	—
Unequivocal PD	Yes and No	PD	—
Any	Yes	PD	—

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

a: ‘Non-CR/non-PD’ is preferred over ‘SD’ for non-target disease because SD is increasingly used as an endpoint for assessment of efficacy in some trials, therefore, to assign this category when no lesions can be measured is not advised.

Table 16-13: Best overall response when confirmation of CR or PR is required

Overall Response First Time-point	Overall Response Subsequent Time-point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR=complete response; NE=non-evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

a: If a CR is truly met at the first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (because the disease must have re-appeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely present and, in fact, the subject had PR, or CR at the first time point. Under this circumstances, the original CR should be changed to PR and the best response is PR.

Response duration

Response duration will be measured from the time that measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent disease or PD is objectively documented.

Stable disease duration

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as a reference the smallest measurements recorded since the start of treatment.

Methods of measurement

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

Clinical lesions - Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken because it is more objective and may also be reviewed at the end of the study.

Chest x-ray - Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT / MRI – CT scan is the best currently available and reproducible method to measure target lesions selected for response assessment. MRI is acceptable in certain situations (e.g., for body scans). CT scans should be performed with cuts of 5 mm or less in slice thickness, contiguously. This applies to the chest, abdomen and pelvis. Head and neck and extremities usually require specific protocols.

Ultrasound - Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy / laparoscopy - The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers - Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated.

Cytology / histology - These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable

disease) and progressive disease.

Bone lesions: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these can be used to confirm the presence or disappearance of bone lesions.

16.9 Estimation of renal function

Estimated glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease (MDRD) equation

The glomerular filtration rate (GFR) will be estimated using the variables serum creatinine, age (years), race, and gender.

The equation does not require weight because the results are reported normalized to 1.73 m2 body surface area, which is an accepted average adult surface area.

All laboratories should be using creatinine (Cr) methods calibrated to be IDMS (isotope dilution mass spectrometry) traceable.

For creatinine in mg/dL; age in years

Men: eGFR (mL/min/1.73 m^2)* = 175 x (serum creatinine)-1.154 x $age^{-0.203}$

Women: eGFR (mL/min/1.73 m^2)* = 175 x (serum creatinine)-1.154 x $age^{-0.203}$ x 0.742

For creatinine in µmol/L; age in years

Men: eGFR (mL/min/1.73 m^2)* = 175 x $(\text{serum creatinine} / 88.4)^{-1.154}$ x $age^{-0.203}$

Women: eGFR (mL/min/1.73 m^2)* = 175 x $(\text{serum creatinine} / 88.4)^{-1.154}$ x $age^{-0.203}$ x 0.742

* For African Americans, multiply by 1.212 (eGFR x 1.212)

The calculator for SI units (for outside the U.S) or for conventional units (for use primarily in the USA) provided by the National Kidney Disease Education Program should be used by the investigator to calculate subject's eGFR (see link below):

http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-SI-units.shtml

http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-conventional-unit.shtml

16.10 New York Heart Association (NYHA) classification

The stages of heart failure will be assessed according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the subject's quality of life.

Table 16-14: New York Heart Association (NYHA) classification

Class	Subject symptoms
Class I (mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

16.11 CYP 3A4 inhibitors and inducers

Table 16-15 provides an overview of strong CYP3A4 inhibitors and inducers (source: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm).

Table 16-15: An overview of strong CYP3A4 inhibitors and inducers

Strong CYP 3A4 Inhibitors	Strong CYP 3A4 Inducers
Boceprevir	Avasimibe
Clarithromycin	Carbamazepine
Conivaptan	Phenytoin
Grapefruit juice	Rifampin
Indinavir	St. John's wort
Itraconazole	
Ketoconazole	
Lopinavir / Ritonavir	
Mibefradil (withdrawn in US)	
Nefazodone	
Nelfinavir	
Posaconazole	
Ritonavir	
Saquinavir	
Telaprevir	
Telithromycin	
Voriconazole	