# Clinical Trial Protocol

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| **Clinical Trial Protocol Number** | EMR100036-002 |
| **Title** | An Open Label, Phase Ia/Ib Trial of the DNA-PK Inhibitor MSC2490484A in Combination with Radiotherapy in Patients with Advanced Solid Tumors |
| **Phase** | Ia/Ib (with an ancillary clinical proof-of-principle part) |
| **IND Number** | CCI |
| **EudraCT Number** | 2015-000673-12 |
| **Coordinating Investigator** | PPD |
| **Sponsor** | Merck KGaA Darmstadt, Germany<br>And, in the USA only:<br>EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), 45A Middlesex Turnpike, Billerica, MA 01821, USA<br>Medical Responsible<br>PPD<br>Merck KGaA Darmstadt<br>Frankfurter Strasse 250<br>64293 Darmstadt, Germany<br>Phone: PPD<br>Fax: Not applicable<br>E-mail: PPD |
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- Confidential -

## Protocol Table of Contents

## Table of In-Text Tables



## Table of In-Text Figures

## List of Abbreviations

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|---|---|
| ADME | Absorption, distribution, metabolism, and elimination |
| AE | Adverse event |
| ADR | Adverse drug reaction |
| ALL | All subjects (analysis set) |
| ALT | Alanine aminotransferase |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate aminotransferase |
| AUC | Area under the concentration-time curve |
| $AUC_{0-\infty}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{0-t}$ | Area under the concentration-time curve from time zero to the time of the last quantifiable concentration |
| $AUC_{\tau}$ | Area under the concentration-time curve over the dosing interval after multiple dosing |
| BCRP | Breast cancer resistance protein |
| BID | Twice daily |
| BSA | Body surface area |
| CI | Confidence interval |
| CL/f | Oral clearance |
| CLss/f | Oral clearance at steady state |
| CNS | Central nervous system |
| cPoP | Clinical proof-of-principle |
| CRO | Contract research organization |
| CRT | Chemoradiotherapy |
| CT | Computed tomography |
| CTCAE | Common terminology criteria for adverse events |

| | |
|---|---|
| ctDNA | Circulating tumor DNA |
| $C_{max}$ | Maximum observed plasma concentration |
| CYP | Cytochrome P450 |
| DE | Dose escalation (analysis set) |
| DLT | Dose limiting toxicity |
| DNA-PK | Deoxyribonucleic acid-dependent protein kinase |
| DSB | Double-strand break |
| ECG | Electrocardiogram |
| ECOG PS | Eastern cooperative oncology group performance status |
| eCRF | Electronic case report form |
| EOT | End of trial |
| ETT | Early treatment termination |
| FAS | Full analysis set |
| FD | Fraction day |
| FIM | First-in-man |
| FT | Feeding tube |
| FU | Follow-up |
| F/W | Fractions per week |
| GCP | Good clinical practice |
| G-CSF | Granulocyte-colony stimulating factor |
| Gy | Gray (derived unit of ionizing radiation dose) |
| HBV | Hepatitis B virus |
| HCG | Human chorionic gonadotropin |
| HCV | Hepatitis C virus |

| | |
|---|---|
| HIV | Human immunodeficiency virus |
| CCI | [redacted] |
| HNSTD | Highest non-severely toxic dose |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| iv | Intravenous |
| MedDRA | Medical dictionary for regulatory activities |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| NCI | National Cancer Institute |
| NOAEL | No observed adverse effect level |
| NSCLC | Non-small cell lung cancer |
| OS | Overall survival |
| PBPK | Population-based pharmacokinetic |
| PEG | Percutaneous endoscopic gastrostomy |
| CCI | [redacted] |
| p-DNA-PK | Phosphorylated DNA-PK |
| PFS | Progression free survival |
| CCI | [redacted] |
| PI3K | Phosphoinositol-3 kinase |
| PiC | Powder in capsule |

| | |
|---|---|
| PK | Pharmacokinetic(s) |
| PPI | Proton pump inhibitor |
| PTD | Post-treatment day |
| QD | Once daily |
| QTcF | Fridericia-corrected QT interval |
| $R_{acc(AUC)}$ | Accumulation ratio for area under the concentration-time curve |
| $R_{acc(Cmax)}$ | Accumulation ratio for maximum concentration |
| RECIST | Response evaluation criteria in solid tumors |
| RP2D | Recommended Phase II dose |
| RT | Radiotherapy |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SAP | Statistical analysis plan |
| SCCHN | Squamous cell carcinoma head and neck |
| SD | Standard deviation |
| SMC | Safety Monitoring Committee |
| SmPC | Summary of product characteristics |
| SoC | Standard of Care |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{1/2}$ | Apparent terminal half-life |
| TEAE | Treatment-emergent adverse event |
| $t_{max}$ | Time to reach maximum observed concentration |
| ULN | Upper limit of normal |
| USA | United States of America |

| | |
|---|---|
| $V_{z/f}$ | Apparent volume of distribution during terminal phase |
| $V_{ss/f}$ | Apparent volume of distribution at steady state |
| WOCBP | Woman of childbearing potential |

# 1 Synopsis

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|---|---|
| **Clinical Trial Protocol Number** | EMR100036-002 |
| **Title** | An Open Label, Phase Ia/Ib Trial of the DNA-PK Inhibitor MSC2490484A in Combination with Radiotherapy in Patients with Advanced Solid Tumors |
| **Trial Phase** | Ia/Ib with an ancillary clinical proof-of-principle (cPoP) part |
| **IND Number** | CCI [redacted] |
| **FDA covered trial** | Yes |
| **EudraCT Number** | 2015-000673-12 |
| **Coordinating Investigator** | PPD [redacted] |
| **Sponsor** | Merck KGaA Darmstadt, Germany<br>And, in the United States of America (USA) only, EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), 45A Middlesex Turnpike, Billerica, MA 01821, USA |
| **Trial centers/countries** | Approximately 12 sites in approximately 4 countries in Europe and approximately 8 sites in the USA. |
| **Planned trial period (first subject in-last subject out)** | 31 May 2015 – 02 August 2021 |
| **Trial Registry** | EudraCT, ClinicalTrials.gov |

**Objectives**

**Primary objectives:**

- Phase Ia: (dose escalation):
  - (Arm A) To determine the maximum tolerated dose (MTD) and a recommended Phase II dose (RP2D) for M3814 (also referred to as MSC2490484A) in combination with fractionated palliative radiotherapy (RT) for tumors or metastases localized in the head and neck region or thorax (3 Gy x 10; 5 fractions per week [F/W]).

- (Arm B) To determine the MTD and a RP2D for M3814 in combination with curatively intended chemoradiotherapy (CRT: 2 Gy x 33 to 35; 5 F/W with concurrent cisplatin) in treatment-naïve subjects with local/locally advanced SCCHN.

- Phase Ib (disease specific cohort expansion):
  - (Arm A) To evaluate the safety and tolerability of M3814 in combination with fractionated RT (2 Gy x 33; 5 F/W) in treatment-naïve subjects with Stage III A/B non-small cell lung cancer (NSCLC) not eligible for concurrent chemoradiation
  - (Arm B) To evaluate the safety and tolerability of M3814 in combination with CRT (2 Gy x 33 to 35; 5 F/W with concurrent cisplatin) in subjects with treatment-naïve SCCHN.

**Secondary objectives:**

- Phase Ia (dose escalation):
  - To evaluate the safety profile and tolerability of M3814 in combination with RT (Arm A) and CRT (Arm B)
  - To explore the antitumor activity of M3814 in combination with RT (Arm A) and CRT (Arm B).
- Phase Ib (disease specific cohort expansion):
  - To explore the efficacy in terms of overall response rate, progression free survival (PFS) and overall survival (OS) of M3814 in combination with RT (Arm A) or in combination with CRT (Arm B), and local/local regional tumor control (Arm B)
- Phase Ia, Phase Ib, and the ancillary cPoP part of the trial: To assess the pharmacokinetics (PK) of M3814.

CCI [redacted]

CCI

**Methodology:** This is a combined Phase Ia/Ib, open label, dose escalation and dose expansion trial designed to explore the safety, tolerability, PK and PD profile, and clinical activity of M3814 in combination with RT/CRT, and to determine the MTD and a RP2D for M3814 in combination with RT/CRT. An ancillary cPoP part of the trial will be conducted in parallel with the Phase Ia/Ib core trial to explore the PD effect of M3814 in combination with RT on target engagement in tumor tissue.

In the Phase Ia part of the trial, previously treated subjects with locally advanced disease (any tumor or metastases including lymphomas) localized in the head and neck region or thorax that is not amenable to surgical therapy or with standard systemic therapy with an indication for palliative RT (30 Gy in 10 fractions) will be included in Arm A. After the first dose level in Arm A has been completed, a second dose escalation arm (Arm B) will be initiated in treatment-naïve subjects with SCCHN, who are eligible for fractionated RT (66 to 70 Gy in 33 to 35 fractions) with concurrent cisplatin. The dose escalation of M3814 determined by the Safety Monitoring Committee (SMC) will be guided by the Bayesian logistic model with overdose control.

In the Phase Ib part, each arm from Phase Ia will have an expansion cohort. After establishment of RP2D in Arm A, subjects with treatment-naïve Stage III A/B NSCLC, not eligible for surgical resection or concurrent chemoradiation, will be given 66 Gy in 33 fractions. The dose of M3814 for the first 3 subjects will be established from the available data in both arms of Phase Ia. In case a RP2D in Arm B has been established before a RP2D in Arm A, then the expansion cohort for Arm A can be initiated at that dose. In case a RP2D has been established in Arm A only, then the first 3 subjects in the expansion cohort for Arm A will be treated at

one dose level below the RP2D. The SMC will determine if it is safe to escalate the dose. The expansion cohort for Arm B will include treatment-naïve subjects with SCCHN, as specified in Phase Ia, and will be given the same CRT (66 to 70 Gy in 33 to 35 fractions with concurrent cisplatin) in combination with M3814 at the RP2D established in Phase Ia Arm B.

In the ancillary cPoP part of the trial, subjects with at least 2 (sub)cutaneous tumor/metastases of any type (at least 2 cm apart) with an indication for single high dose palliative RT will be included. The dose of M3814 will be in the range of 100 to 400 mg once daily (QD).

The current trial initially started to investigate M3814 by use of a powder-in-capsule (PiC) formulation. While the dose escalation phase of Phase Ia was ongoing, a new CCI tablet formulation of M3814 became available. The CCI tablet will be introduced and evaluated in this trial.

**Screening period**

After providing informed consent for the trial and the pharmacogenetic (PGx) analysis, the eligibility of trial subjects will be established according to the protocol-defined inclusion and exclusion criteria during a maximum 21-day Screening Period (screening and baseline evaluations). Once all screening procedures have been completed and it has been confirmed that a subject meets all the eligibility criteria, the subject will be enrolled into the trial and enter the treatment period.

**Treatment periods**

Throughout the treatment period, subjects in all cohorts will attend regular trial visits for dosing, safety evaluations and blood sampling for PK and PD.

Phase Ia

Following completion of the screening and baseline evaluations, subjects enrolled in the Phase Ia part of the trial will receive treatment with a capsule formulation of M3814 at a starting dose of 100 mg QD for Arm A and 50 mg QD for Arm B, which will be given 1.5 hours (± 30 minutes) before each RT fraction (3 Gy) for up to 10 fractions (Arm A) or 2 Gy for 33 to 35 fractions (Arm B).

In both arms, dose escalation will continue with the M3814 capsule formulation from 100 mg/day (Arm A) or 50 mg/day (Arm B) up to a maximum dose of 800 mg/day until one of the following stopping rules apply: a maximum number of 30 subjects are included, more than three cohorts are assigned to the same dose level or the estimate for dose limiting toxicity (DLT) probability of the MTD reaches sufficient precision. It is anticipated that up to 30 evaluable subjects (10 cohorts of 3 subjects) may be needed in each arm in order to determine the MTD of M3814.

The tablet will be introduced first in Phase Ia Arm A in combination with RT. Subjects will receive the tablet at a starting dose of 100 mg QD. Safety, tolerability and exposure data already generated with the capsule formulation of M3814 in combination with RT will guide the establishment of the RP2D with the tablet. In addition, an intra-individual comparison of M3814 PK between the tablet and capsule will be performed in Phase Ia Arm A. These PK

results together with available safety and tolerability results generated with the capsule in Phase Ia Arm B will guide the switch from the capsule to the tablet in combination with cisplatin and RT in Phase Ia Arm B. Depending on the availability of the tablet data, the dose escalation with the capsule is going to be stopped and substituted with the tablet.

It is planned to use the tablet formulation in the dose expansion cohorts in Phase Ib.

Phase Ib

Following completion of the screening and baseline evaluations, treatment-naïve subjects with Stage III A/B NSCLC enrolled in the Phase Ib part of the trial (expansion cohort for Arm A - NSCLC) will receive M3814, to be given 1.5 hours (± 30 minutes) before each RT (2 Gy) fraction for up to 33 fractions. The dose of M3814 for the first 3 subjects will be established from the available data in both arms of the Phase Ia part of the trial. Based on the safety profile the SMC will decide if the dose can be escalated. In the expansion cohort for Arm B, subjects with treatment-naïve SCCHN will receive M3814, to be given 1.5 hours (± 30 minutes) before each RT (2 Gy) fraction for 33 to 35 fractions, with concurrent cisplatin, at the RP2D established in Phase Ia (Arm B).

It is planned to enroll a total of up to 27 evaluable subjects with Stage III A/B NSCLC in the Phase Ib part of the trial (expansion cohort for Arm A), and the expansion cohort for Arm B is planned to enroll a total of up to 27 evaluable subjects with SCCHN.

Ancillary cPoP part of the trial

Following completion of the screening and baseline evaluations, subjects enrolled in the ancillary cPoP part of the trial will receive a single high dose of RT (10-25 Gy) on Lesion 1 on Day 1 and on Lesion 2 on Day 2. A single dose of M3814 will be administered on Day 2, 1.5 hours (± 30 minutes) before the start of RT. Three fixed dose levels are planned (100 mg, 200 mg, and 400 mg). Additional doses might be opened upon SMC decision.

The ancillary cPoP part of the trial will initially be conducted with the capsule; however, additional cohorts of M3814 (CCI formulation) may be introduced. The starting dose and subsequent dose levels of M3814 (CCI formulation) will be defined by the SMC based on PK and safety data generated in ongoing clinical studies evaluating the safety, tolerability, PK, and PD of M3814 (CCI formulation).

It is planned to enroll 11 subjects with (sub)cutaneous tumor/metastases in the ancillary cPoP part of the trial using M3814 capsule formulation and approximately 12 additional subjects with (sub)cutaneous tumor/metastases using M3814 CCI formulation.

**Follow-up periods**

Phase Ia/Ib

The follow-up period for all subjects in the Phase Ia and Ib parts of the trial will consist of the following:

- DLT Period: A 5-week (Arm A) or 12-week (Arm B) DLT period after the first dose of M3814 for the evaluation of 'acute' systemic and local toxicity in all subjects in Phase Ia, and a 12-week DLT period after the first dose of M3814 in the first 3 subjects of the safety run-in part in the NSCLC expansion cohort during Phase Ib (Arm A)

- Short-term Safety Follow-up: A follow-up period of 30 days after the end of RT for evaluation of safety
- Mid-term Safety Follow-up: A safety follow-up period of 3 months after the end of RT to evaluate late signs of RT-induced toxicity on normal surrounding tissues
- Long-term Safety Follow-up: A safety follow-up period until 12 months after end of RT to evaluate late signs of RT-induced toxicity on normal surrounding tissues
- Survival Follow-up: A follow-up period that will continue until 12 months after the last subject has stopped RT/CRT.

Ancillary cPoP part of the trial

A follow-up period of 30 days after the end of the RT/M3814 for evaluation of safety. Subjects will be permitted to receive any indicated therapeutic modality as soon as clinically indicated after Day 10.

**Dose escalation**

M3814 dose escalation will not proceed to the next dose level until all subjects have completed the DLT period.

Phase Ia

A Bayesian two-parameter logistic regression model with overdose control will be used to assist the SMC with dose selection during the Phase Ia dose escalation. Cohorts of 3 subjects each will be treated at the same dose level (capsule starting dose: 100 mg QD for Arm A and 50 mg QD for Arm B). The model incorporates prior information (from nonclinical data) and observed information from each completed cohort (and data from all previous cohorts) to provide a recommended dose for the next cohort. A preselected set of acceptable doses are considered by the model, however doses which are not part of the prespecified set may be chosen as well. The model ensures that recommended doses correspond to a probability of less than 25% that the true DLT rate is more than 35% in Arm A and 45% in Arm B. Dose escalation will stop in each arm as soon as the first of the following stopping rules apply: a maximum of 30 subjects are included, more than three cohorts are assigned to the same dose level, or the estimate of DLT probability at the MTD reaches a sufficient precision.

Phase Ib

Following completion of the screening and baseline evaluations, treatment-naïve subjects with Stage III A/B NSCLC enrolled in the Phase Ib part of the trial (Arm A expansion cohort) will receive M3814, to be given 1.5 hours (± 30 minutes) before each RT fraction for 33 fractions. The dose of M3814 for the first 3 subjects will be established from the available data in both arms of the Phase Ia part of the trial.

The dose in the Arm B expansion cohort will be the determined RP2D of M3814 from Phase Ia, Arm B and will be given to subjects with treatment-naïve SCCHN in combination with the same CRT regimen as in Phase Ia (Arm B).

**Doses of M3814 in the ancillary cPoP part of the trial**

Ancillary cPoP part

The single dose of M3814 to be administered on Day 2 of the ancillary cPoP part of the trial is fixed for successive cohorts as shown below:

**Doses of M3814 in the ancillary cPoP part of the trial**

| Dose (mg)[a] | Number of subjects included[b] |
|---|---|
| 100 | 3 |
| 200 | 3 |
| 400 | 3 |
| (> 100 / < 400)[c] | (3) |

cPoP = clinical proof-of-principle; CCI = CCI [redacted] PK = pharmacokinetics; RP2D = recommended Phase II dose; SMC = Safety Monitoring Committee.

a. Additional cohorts of M3814 (CCI formulation) may be introduced. The starting dose and subsequent dose levels of M3814 (CCI formulation) will be defined by the SMC based on PK and safety data generated in ongoing clinical studies evaluating the safety, tolerability, PK, and pharmacodynamics of M3814 (CCI formulation).

b. At the RP2D an additional 2 subjects will be included making 5 subjects at the RP2D.

c. Additional doses might be opened upon SMC decision.

**Planned number of subjects:** Up to 155 evaluable subjects will be enrolled in this trial: approximately 78 evaluable subjects in Phase Ia part; up to 54 evaluable subjects in Phase Ib dose expansion part; and approximately 23 subjects in the ancillary cPoP part of the trial. Considering a drop-out rate of 10% for subjects not evaluable for DLT assessment in Phase Ia, approximately 165 subjects need to be included in the trial.

**Primary endpoints:**

- Phase Ia (Arm A):
  - Occurrence of DLT up to 5 weeks after the first dose of M3814 in combination with palliative fractionated RT.
- Phase Ia (Arm B):
  - Occurrence of DLT up to 12 weeks after the first dose of M3814 in combination with standard CRT (with cisplatin) with curative intent.
- Phase Ib (Arm A) – first 3 subjects:
  - Occurrence of DLT up to 12 weeks after the first dose of M3814 in combination with curatively intended fractionated RT.
- Phase Ib: Safety and tolerability as follows:
  - Occurrence of treatment-emergent adverse events (TEAEs) (severity graded according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v4.03).
  - Results of laboratory tests, vital signs, electrocardiograms (ECGs).

**Secondary endpoints:**

- Phase Ia (Arm A and Arm B): Safety endpoints:
  - Occurrence of TEAEs (severity graded according to the NCI CTCAE v4.03)

- Results of laboratory tests, vital signs, ECGs.

- Efficacy parameters
  - Best overall response based on tumor evaluations made by Investigator in accordance with RECIST (Response evaluation criteria in solid tumors) v1.1
  - Tumor size measurement based on Investigator assessment in accordance with RECIST v1.1
  - PFS time defined as time from the first dose of trial treatment to progressive disease (per RECIST v1.1) based on the Investigator assessment or death from any cause, and local/local regional tumor control (Phase Ib, Arm B expansion cohort)
  - OS time defined as time from the first dose of trial treatment to the date of death from any cause.

**Pharmacokinetic endpoints - capsule:** Plasma PK parameters of M3814 for Phase Ia part:

a. Fraction Day 1 – maximum observed plasma concentration ($C_{max}$), time to reach maximum observed concentration ($t_{max}$), area under the concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration ($AUC_{0-t}$), AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal half-life ($t_{1/2}$), oral clearance (CL/f), apparent volume of distribution during terminal phase (Vz/f)

b. Fraction Day 10 - $C_{max}$, $t_{max}$, AUC over the dosing interval after multiple dosing ($AUC_{\tau}$), $AUC_{0-\infty}$, $t_{1/2}$, oral clearance at steady state (CLss/f), apparent volume of distribution at steady state (Vss/f), accumulation ratio for AUC curve ($R_{acc}[AUC]$), accumulation ratio for maximum concentration ($R_{acc}[C_{max}]$).

**Pharmacokinetic endpoints - tablet:** Plasma PK parameters of M3814 for Phase Ia part:

a. Fraction Day 1 – $C_{max}$, $t_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $t_{1/2}$, CL/f, Vz/f

b. Fraction Day 6 - $C_{max}$, $t_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $t_{1/2}$, CL/f, Vz/f

c. Fraction Day 10 - $C_{max}$, $t_{max}$, $AUC_{\tau}$, $AUC_{0-\infty}$, $t_{1/2}$, CLss/f, Vss/f, $R_{acc}[AUC]$, $R_{acc}[C_{max}]$.

Population PK parameters for Phase Ib and the ancillary cPoP part of the trial will be reported in a separate PK report, which will not be part of the Clinical Trial Report for this trial.

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[redacted]

**Diagnosis and key inclusion and exclusion criteria:**

Inclusion criteria

- **Phase Ia part**: advanced solid tumors or metastases including lymphoma localized in the head and neck region or thorax with an indication for fractionated palliative RT (Arm A); or treatment-naïve SCCHN eligible for fractionated curatively intended RT with concurrent cisplatin (Arm B)
- **Phase Ib part**: treatment-naïve Stage III A/B NSCLC not eligible for surgical resection or concurrent chemoradiation (Arm A expansion cohort) or treatment-naïve SCCHN eligible for fractionated curatively intended RT with concurrent cisplatin (Arm B expansion cohort)
- **Ancillary cPoP part**: any tumor with at least 2 (sub)cutaneous tumor/metastases at least 2 cm apart which are RT naïve with an indication for high dose palliative RT
- Availability of archival tumor material, either as a block or slides (Phase Ia and Ib). If no archival material is available then a fresh biopsy should be taken
- Willing to have tumor biopsies collected in the ancillary cPoP part of the trial
- Measurable or evaluable disease by RECIST v1.1 (not required for the ancillary cPoP part of the trial)
- Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq 1$
- Life expectancy of $\geq 3$ months (Phase Ia, Arm A) or $\geq 6$ months (Phase Ia, Arm B and Phase Ib)

- Female subjects of childbearing potential and male subjects with female partners of childbearing potential must be willing to avoid pregnancy.

Main exclusion criteria for Phase Ia and Phase Ib:

- Chemotherapy, immunotherapy, hormonal therapy, biologic therapy, or any other anticancer therapy or IMP within 28 days of first trial drug intake for Phase Ia subjects, and any prior therapy for Phase Ib subjects. For subjects with rapidly growing tumors localized in the head and neck region or thorax where the treating physician cannot wait for 28 days, inclusion may take place if there is no residual toxicity from previous treatment (maximum CTCAE Grade 1)
- Prior RT to the same region within 12 months (Phase Ia, Arm A; subjects with tumors localized in the head and neck region or thorax) or at any time previously (Phase Ia, Arm B; treatment-naïve subjects with SCCHN and Phase Ib; treatment-naïve subjects with Stage III A/B NSCLC or SCCHN)
- Extensive prior RT on ≥ 30% of bone marrow reserve as judged by the Investigator or prior bone marrow/stem cell transplantation within 5 years before trial start.
- Poor vital organ functions defined as:
    - Bone marrow impairment as evidenced by hemoglobin <10.0 g/dL, neutrophil count $<1.0 \times 10^9$/L, platelets $<100 \times 10^9$/L
    - Renal impairment as evidenced by serum creatinine >1.5 × upper limit of normal (ULN)
    - Liver function abnormality as defined by total bilirubin >1.5 × ULN or aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >2.5 × ULN (except for subjects with liver involvement, who can have AST/ALT >5 × ULN)
- History of difficulty swallowing, malabsorption or other chronic gastrointestinal disease or conditions that may hamper compliance and/or absorption of the IMP, current use of percutaneous endoscopic gastrostomy (PEG) tubes
- Significant cardiac conduction abnormalities, including a history of long QTc syndrome and/or pacemaker, or impaired cardiovascular function such as New York Heart Association classification score >2.
- Subjects currently receiving (or unable to stop using prior to receiving the first dose of trial drug) medications or herbal supplements known to be potent inhibitors of cytochrome P450 (CYP)3A or CYP2C19 (must stop at least 1 week prior), potent inducers of CYP3A or CYP2C19 (must stop at least 3 weeks prior), or drugs mainly metabolized by CYP3A with a narrow therapeutic index (must stop at least one day prior).
- Subjects currently receiving $H_2$-blocker or proton pump inhibitors (or unable to stop at least 5 days prior to the first treatment).
- If the planned radiation field includes any part of the esophagus and the subject has symptoms of ongoing esophagitis, the subject is not eligible, unless an esophageal endoscopy rules out the presence of esophagitis.

- Subjects where more than 10% of the total esophagus volume receives more than 50% of the prescribed RT dose.

Main exclusion criteria for the ancillary cPoP part of the trial

- History of difficulty swallowing, malabsorption or other chronic gastrointestinal disease or conditions that may hamper compliance and/or absorption of the IMP
- History of any other significant medical disease such as major gastric or small bowel surgery, recent drainage of significant volumes (as per Investigator's judgement) of ascites or pleural effusion or a psychiatric condition that might impair the subject's well-being or preclude full participation in the trial
- Subjects currently receiving (or unable to stop using prior to receiving the first dose of trial drug) medications or herbal supplements known to be potent inhibitors of CYP3A or CYP2C19 must stop at least 1 week prior to taking M3814. Subjects receiving potent inducers of CYP3A or CYP2C19 must stop at least 3 weeks prior to taking M3814. Those receiving drugs mainly metabolized by CYP3A with a narrow therapeutic index as judged by the Investigator (and after optional consultation with the Sponsor) must stop at least one day prior to taking M3814.

**Investigational Medicinal Product - Dose/mode of administration/dosing schedule:**

M3814 will be provided as PiC formulation of 10 mg, 50 mg, and 100 mg for oral administration.

The initial starting dose will be 100 mg QD (Arm A) or 50 mg QD (Arm B) administered 1.5 hours (± 30 minutes) before RT. In the ongoing first-in-man (FIM) trial (EMR100036-001), the starting dose was 100 mg QD and no DLTs were seen at this dose level. Furthermore, in the FIM trial additional cohorts were treated at 200 mg QD, 150 mg twice daily (BID), and 200 mg BID and no DLTs were seen at any of these dose levels.

The criteria for dose escalation are based on the occurrence of adverse events (AEs) and/or DLTs that are unrelated to underlying conditions and/or to concomitant medication during the DLT period in evaluable subjects in each cohort. The DLT window allows an evaluation of acute toxicity. However, RT and the combination of RT and M3814 can also give rise to later toxicities. A 3-month mid-term safety follow-up will be performed in all subjects in the Phase Ia part of the trial and, once available, these data will also guide subsequent dose escalation and the establishment of the RP2D in each arm. Available PK and PD data will also be taken into consideration.

In the ancillary cPoP part of the trial, the doses are fixed at 100 mg, 200 mg, and 400 mg. Additional doses might be opened upon SMC decision.

The ancillary cPoP part of the trial will initially be conducted with the capsule formulation; however, additional cohorts of M3814 (CCI formulation) may be introduced. The starting dose and subsequent dose levels of M3814 (CCI formulation) will be defined by the SMC based on PK and safety data generated in ongoing clinical studies evaluating the safety, tolerability, PK, and PD of M3814 (CCI formulation).

**CCI (CCI tablet formulation of M3814:**

M3814 will be provided as CCI tablet formulation of 50 mg, for oral administration. Dosing schedule of the tablet formulation follows the description given for the capsule formulation above. The tablet formulation will be initially assessed in Phase Ia Arm A taking into account the available safety, tolerability and PK results from the capsule. Standard 3+3 dose escalation design criteria will apply. Evaluation of single dose PK data after administration of the tablet and the capsule in the same subject will support the selection of tablet doses in Phase Ia Arm B, the Phase Ib parts and in the additional cohorts of M3814 in the ancillary cPoP part of the trial.

**Concurrent cisplatin - Dose/mode of administration/dosing schedule:**

Concurrent cisplatin will be administered in combination with the IMP in subjects with SCCHN included in Phase Ia Arm B and the SCCHN expansion cohort in Phase Ib. The dose and dose regimen of cisplatin is to be applied in line with current medical guidelines (NCCN, ACCP/ASCO, and ESMO) with reference to the Standard of Care (SoC) for concurrent CRT with cisplatin in the treatment of subjects with SCCHN. Cisplatin will be given twice at a dose of 100 $mg/m^2$ or weekly at a dose of 40 $mg/m^2$.

**Planned trial and treatment duration per subject:**

Treatment duration is expected to be approximately 2 weeks (Arm A) or 7 weeks (Arm B) for the Phase Ia part, 6-7 weeks for the Phase Ib part, and 2 days for the ancillary cPoP part.

**Statistical methods:**

In the Phase Ia part, for each arm (A and B) the sample size will depend on the number of DLTs observed at the different dose levels and the number of tested or expanded dose levels for M3814. Subjects will be enrolled in cohorts of 3 subjects.

The Phase Ib part consists of one expansion cohort per arm from the Phase Ia part. For Arm A, the expansion cohort will explore the activity of M3814 combined with RT in treatment-naïve subjects with Stage III A/B NSCLC. The cohort will enroll up to 27 evaluable subjects including the safety run-in part, bringing the anticipated maximum sample size for the Phase Ia/Ib parts to 75 subjects for Arm A. A sample size of 27 evaluable subjects will enable the lower limit of a 2-sided 95% confidence interval (CI) for the response rate to extend no further than an absolute 20% from the expected proportion of 50%, thereby ensuring the lower limit is no less than the historical control of 30% in treatment-naïve subjects with Stage III A/B NSCLC.

For Arm B, the anticipated sample size in the escalation part is 30 participants (together for tablet and capsule). The expansion cohort will explore the safety, tolerability and efficacy of M3814 combined with CRT (with cisplatin) in treatment-naïve subjects with SCCHN. A sample size of up to 27 evaluable subjects will be enrolled to confirm safety and tolerability of the combination. Together, this brings the anticipated sample size for the Phase Ia/Ib parts to 57 subjects for Arm B.

For the ancillary cPoP part of the trial conducted in parallel with the Phase Ia part, a fixed number of 3 subjects will be enrolled at the two lower fixed dose levels and 5 subjects will be enrolled at the RP2D. Assuming a correlation between the fold induction of the marker and the dose is 0.69, the power of detecting a linear relationship is 80% with an alpha-level of 5% (2-sided). In case the PD results don't allow detection of sufficient modulation of target engagement i.e., a clear dose/effect relationship between levels in pre- and on treatment tumor biopsies, additional dose

level(s) could be explored upon SMC decision according to the findings during the escalation phase in Phase Ia. Approximately 12 additional subjects may be enrolled in the ancillary cPoP part of the trial using M3814 CCI formulation, thus leading to a maximum sample size in the ancillary cPoP part of 23.

The anticipated total number of evaluable subjects to be included in the three parts of the trial with additional cohorts in the ancillary cPoP part of the trial is therefore 155. Considering a drop-out rate of 10% for subjects not evaluable for DLT assessment in Phase Ia, approximately 165 subjects need to be enrolled in the trial.

For the Phase Ia part, the number and proportion of subjects experiencing a DLT will be reported by formulation and dose level, based on the observation of DLTs up to 5 weeks (Arm A) or 12 weeks (Arm B) after the first dose of M3814 taking into account the known toxicities with RT alone.

For the safety run-in part of Phase Ib (first 3 subjects in Arm A), the number of subjects experiencing a DLT up to 12 weeks after the first dose of M3814 will also be reported. Subjects included in the run-in part will be analyzed separately from the remaining subjects of Phase Ib.

All secondary endpoints will be summarized by mean of descriptive statistics including 95% CI by dose level and overall, unless otherwise stated. Response rate will be calculated, and PFS and OS will be evaluated for the expansion cohort only.

Adverse events will be coded according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using the CTCAE (v4.03) toxicity grades. Adverse events related to the trial medication will be defined as any AE considered related to M3814. In addition, missing classifications concerning trial medication relationships will be considered related to the trial drug. Subjects who terminate treatment will be displayed in a by-subject listing, and summarized by primary withdrawal reason for each treatment group. All reported deaths during therapy and deaths within 30 days after last dose of trial treatment will be tabulated and the primary cause of death will be reported (for all subjects enrolled). Laboratory results will be classified by grade according to the CTCAE v4.03. The worst on-trial grades after the first dose of trial treatment will be summarized.

**Table 1 Schedule of Assessments – Phase Ia (Arm A): Capsule Cohorts**

| Trial Periods | Screening | DLT Evaluation Period | | | | | Short-term Safety FU | Mid-term Safety FU | Long-term Safety FU | Survival FU/EOT[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Treatment Period (M3814 + RT) | | | | DLT Period | | | | |
| **Trial Days** | **Day -21 to Day -1** | **FD 1 to FD 10** | | | | **PTD 1 to 21** | **PTD 22 to 30** | **PTD 1 to 90** | **PTD 31 to 365** | **PTD 181 to 365** |
| **M3814 RT 3 Gy x 10 (5 F/W)[b]** | - | X X | | | | | - | | | |
| **Visit Days** | **-21 to -1** | **FD1** | **FD2** | **FD6** | **FD10[c]/ ETT** | **PTD 8, 15** | **PTD 22[d], 30** | **PTD 84** | **PTD 42, 126, 168, 180, 210[x], and 312[x]** | **PTD 270, 365** |
| **Visit Window (days)** | - | - | | - | - | ±2 | ±2 | ±7 | ±7 | ±7 |
| Signed informed consent | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical history | X | | | | | | | | | |
| Serum β-HCG pregnancy test (if applicable) | X | | | | | | PTD 30 only | | | |
| Infection screen (hepatitis B and C), optional HIV test[e] | X | | | | | | | | | |
| Vital signs[f] | X[g] | X | | X | X | X | X | X | X | X[h] |
| Physical examination | X | X | | X | X | X | X | X | X | X[i] |
| Clinical examination of bleeding | X | X | | X | X | X | X | | | |
| Esophageal endoscopy (if relevant) | X | | | | | | | | | |
| Evaluation of all tissues in RT area | | | | X | X | X | X | X | X | X |
| ECOG PS | X | | | | X | X | PTD 30 only | X | X | X[i] |

| Trial Periods | Screening | DLT Evaluation Period | | | | | Short-term Safety FU | Mid-term Safety FU | Long-term Safety FU | Survival FU/EOT[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Treatment Period (M3814 + RT) | | | | DLT Period | | | | |
| **Trial Days** | Day -21 to Day -1 | FD 1 to FD 10 | | | | PTD 1 to 21 | PTD 22 to 30 | PTD 1 to 90 | PTD 31 to 365 | PTD 181 to 365 |
| **M3814 RT 3 Gy x 10 (5 F/W)[b]** | - | X X | | | | | - | | | |
| **Visit Days** | -21 to -1 | FD1 | FD2 | FD6 | FD10[c]/ ETT | PTD 8, 15 | PTD 22[d], 30 | PTD 84 | PTD 42, 126, 168, 180, 210[x], and 312[x] | PTD 270, 365 |
| **Visit Window (days)** | - | - | | - | - | ±2 | ±2 | ±7 | ±7 | ±7 |
| Adverse event assessment | X | X | | X | X | X | X | X[j] | X[j] | X[j] |
| Concomitant medication | X | X | | X | X | X | X | | | |
| Hematology[k] | X | X | | X | X | X | X | | | |
| Serum chemistry and coagulation[l] | X | X | | X | X | X | X | | | |
| Urinalysis (dipstick)[m] | X | | | | X | X | PTD 30 only | | | |
| 12-lead ECG (including QTcF)[n] | X | X[o] | | | X[p] | | | | | |
| Tumor assessment (RECIST)[q] | X | | | | | | | X[r] | X[h, r] | X[h] |
| PK blood samples[s] | | X | X[t] | X | X | | | | | |
| Archival tumor material[u] | X | | | | | | | | | |
| CCI [redacted] | | | | | | | | | | |
| Survival | | | | | | | | | | X[y] |

AE = adverse event; CT = computed tomography; CCI [redacted]; DLT= dose limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EOT = End of Trial; ETT = Early Treatment Termination; FD = fraction day; FU = follow-up; F/W= fraction per week; Gy = Gray; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PD = pharmacodynamics; CCI [redacted]; PK = pharmacokinetics; PTD = Post-treatment Day; QTcF = Fridericia-corrected QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiotherapy; SMC = Safety Monitoring Committee.

Note: Fraction Day (FD) (days when RT and M3814 is given). Post-treatment Day (PTD) (days in the period starting as of end of the treatment period until 1 year later).

a. All subjects will be followed up for response until 12 months after the last subject has stopped RT/CRT, or earlier due to any reason whereby tumor assessments are no longer applicable (e.g., if a new treatment is started, withdrawal of consent). The reason for early discontinuation should be captured in the source document. If EOT occurs before PTD 365, all assessments must be done as planned for PTD 365. After completing the PTD 365 visit, subjects will be followed up for survival via phone call every 3 months, wherever possible.
b. RT to be given 1.5 hours (± 30 minutes) after dosing.
c. FD10 is the day of the last dose of RT. In case of premature withdrawal from the trial during the treatment period, the investigations scheduled for the visit on FD10 should be performed. In such cases this visit will be considered the Early Treatment Termination visit. If FD10 is on a Friday, PK, PD, safety laboratory, and urinalysis sampling must be done on FD9.
d. All AEs will be collected from FD1 up to PTD 21 to evaluate the occurrence of DLTs.
e. Hepatitis B and C testing to be performed at Screening unless obtained within 3 months prior to Screening. Screening for HIV will be performed according to local practice and local regulatory guidance.
f. Heart rate, diastolic and systolic blood pressure, body temperature, and body weight. See Section 7.4.4 for details.
g. Height measured at Screening only.
h. Only required if subject has not started a new antitumor treatment. If a new treatment is started, the date (and regimen) must be reported in the eCRF.
i. Physical exam will report findings in the irradiated area during all FU periods.
j. Evaluation of ongoing treatment-emergent adverse events.
k. See Table 15 for details of hematology tests.
l. See Table 15 for details of serum chemistry tests.
m. Urinalysis: dipstick followed by microscopic examination if abnormal results.
n. 12-lead resting ECG in triplicate.
o. 12-lead ECG to be performed predose and once at 2 to 3 hours postdose.
p. 12-lead ECG to be performed at 2 hours postdose.
q. Tumor imaging by CT or MRI at baseline to document extent of lesions according to RECIST v1.1. Baseline tumor evaluation can be up to 28 days old when treatment starts.
r. Tumor assessments to be done at long-term safety FU (every 6 weeks during Day 31-180 [4 assessments]) and during survival FU (every 13 weeks during Day 181-365 [2 assessments]). Tumor assessment will not be repeated on PTD 180.
s. PK samples will be collected as detailed in Table 9. Sampling schedule may be changed by the SMC based on emerging data. See Section 7.5.1 for details.
t. Predose only.
u. Mandatory archival tumor materials sampled before start of the treatment (most recent materials available). If no archival tumor material is available a fresh biopsy must be taken.

CCI [redacted]

x. PTD 210 and 312 will consist of phone calls to evaluate long term RT toxicity. No other assessments will be performed at these visits.
y. Can be followed up via phone call every 3 months.

**Table 2 Schedule of Assessments – Phase Ia (Arm A): Tablet Cohorts**

| Trial Periods | Screening | DLT Evaluation Period | | | | | | Short-term Safety FU | Mid-term Safety FU | Long-term Safety FU | Survival FU/EOT[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Treatment Period (M3814 + RT) | | | | | DLT Period | | | | |
| **Trial Days** | Day -21 to Day -1 | FD 1 to FD 10 | | | | | PTD 1 to 21 | PTD 22 to 30 | PTD 1 to 90 | PTD 31 to 365 | PTD 181 to 365 |
| **M3814 Tablet[y]** | - | X | | | X | | | - | | | |
| **M3814 Capsule** | | | | X | | | | | | | |
| **RT 3 Gy x 10 (5 F/W)[b]** | - | X | | | | | | - | | | |
| **Visit Days** | -21 to -1 | FD1 | FD2 | FD6[z] | FD7 | FD10[c]/ ETT | PTD 8, 15 | PTD 22[d], 30 | PTD 84 | PTD 42, 126, 168, 180, 210[aa], and 312[aa] | PTD 270, 365 |
| **Visit Window (days)** | - | - | | - | | - | ±2 | ±2 | ±7 | ±7 | ±7 |
| Signed informed consent | X | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | | |
| Demography | X | | | | | | | | | | |
| Medical history | X | | | | | | | | | | |
| Serum β-HCG pregnancy test (if applicable) | X | | | | | | | PTD 30 only | | | |
| Infection screen (hepatitis B and C), optional HIV test[e] | X | | | | | | | | | | |
| Vital signs[f] | X[g] | X | | X | | X | X | X | X | X | X[h] |
| Physical examination | X | X | | X | | X | X | X | X | X | X[i] |
| Clinical examination of bleeding | X | X | | X | | X | X | X | | | |

| Trial Periods | Screening | DLT Evaluation Period | | | | | | Short-term Safety FU | Mid-term Safety FU | Long-term Safety FU | Survival FU/EOT[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Treatment Period (M3814 + RT) | | | | | DLT Period | | | | |
| **Trial Days** | **Day -21 to Day -1** | **FD 1 to FD 10** | | | | | **PTD 1 to 21** | **PTD 22 to 30** | **PTD 1 to 90** | **PTD 31 to 365** | **PTD 181 to 365** |
| **M3814 Tablet[y]** | - | X | | X | | | | - | | | |
| **M3814 Capsule** | | | X | | | | | | | | |
| **RT 3 Gy x 10 (5 F/W)[b]** | - | X | | | | | | - | | | |
| **Visit Days** | **-21 to -1** | **FD1** | **FD2** | **FD6[z]** | **FD7** | **FD10[c]/ ETT** | **PTD 8, 15** | **PTD 22[d], 30** | **PTD 84** | **PTD 42, 126, 168, 180, 210[aa], and 312[aa]** | **PTD 270, 365** |
| **Visit Window (days)** | - | - | | - | | - | ±2 | ±2 | ±7 | ±7 | ±7 |
| Esophageal endoscopy (if relevant) | X | | | | | | | | | | |
| Evaluation of all tissues in RT area | | | | X | | X | X | X | X | X | X |
| ECOG PS | X | | | | | X | X | PTD 30 only | X | X | X[i] |
| Adverse event assessment | X | X | | X | | X | X | X | X[j] | X[j] | X[j] |
| Concomitant medication | X | X | | X | | X | X | X | | | |
| Hematology[k] | X | X | | X | | X | X | X | | | |
| Serum chemistry and coagulation[l] | X | X | | X | | X | X | X | | | |
| Urinalysis (dipstick)[m] | X | | | | | X | X | PTD 30 only | | | |
| 12-lead ECG (including QTcF)[n] | X | X[o] | | | | X[p] | | | | | |
| Tumor assessment (RECIST)[q] | X | | | | | | | | X[r] | X[h, r] | X[h] |

| Trial Periods | Screening | DLT Evaluation Period | | | | | | Short-term Safety FU | Mid-term Safety FU | Long-term Safety FU | Survival FU/EOT[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Treatment Period (M3814 + RT) | | | | | DLT Period | | | | |
| Trial Days | Day -21 to Day -1 | FD 1 to FD 10 | | | | | PTD 1 to 21 | PTD 22 to 30 | PTD 1 to 90 | PTD 31 to 365 | PTD 181 to 365 |
| M3814 Tablet[y] | - | X | | | X | | | - | | | |
| M3814 Capsule | | | | X | | | | | | | |
| RT 3 Gy x 10 (5 F/W)[b] | - | X | | | | | | - | | | |
| Visit Days | -21 to -1 | FD1 | FD2 | FD6[z] | FD7 | FD10[c]/ ETT | PTD 8, 15 | PTD 22[d], 30 | PTD 84 | PTD 42, 126, 168, 180, 210[aa], and 312[aa] | PTD 270, 365 |
| Visit Window (days) | - | - | | - | | - | ±2 | ±2 | ±7 | ±7 | ±7 |
| PK blood samples[s] | | X | X[t] | X | X[t] | X | | | | | |
| Archival tumor material[u] | X | | | | | | | | | | |
| CCI | | | | | | | | | | | |
| Survival | | | | | | | | | | | X[x] |

AE = adverse event; CT = computed tomography; CRT = chemoradiotherapy; CCI; DLT = dose limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EOT = End of Trial; ETT = Early Treatment Termination; FD = fraction day; FU = follow-up; F/W = fraction per week; Gy = Gray; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; CCI; CCI; PK = pharmacokinetics; PTD = Post-treatment Day; QTcF = Fridericia-corrected QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiotherapy; SMC = Safety Monitoring Committee.

Note: Fraction Day (FD) (days when RT and M3814 is given). Post-treatment Day (PTD) (days in the period starting as of end of the treatment period until 1 year later).

a. All subjects will be followed up for response until 12 months after the last subject has stopped RT/CRT, or earlier due to any reason whereby tumor assessments are no longer applicable (e.g., if a new treatment is started, withdrawal of consent). The reason for early discontinuation should be captured in the source document. If EOT occurs before PTD 365, all assessments must be done as planned for PTD 365. After completing the PTD 365 visit, subjects will be followed up for survival via phone call every 3 months, wherever possible.
b. RT to be given 1.5 hours (± 30 minutes) after dosing.
c. FD10 is the day of the last dose of RT. In case of premature withdrawal from the trial during the treatment period, the investigations scheduled for the visit on FD10 should be performed. In such cases this visit will be considered the Early Treatment Termination visit. If FD10 is on a Friday, PK, PD, safety laboratory, and urinalysis sampling must be done on FD9.
d. All AEs will be collected from FD1 up to PTD 21 to evaluate the occurrence of DLTs.
e. Hepatitis B and C testing to be performed at Screening unless obtained within 3 months prior to Screening. Screening for HIV will be performed according to local practice and local regulatory guidance.
f. Heart rate, diastolic and systolic blood pressure, body temperature, and body weight. See Section 7.4.4 for details.
g. Height measured at Screening only.
h. Only required if subject has not started a new antitumor treatment. If a new treatment is started, the date (and regimen) must be reported in the eCRF.
i. Physical exam will report findings in the irradiated area during all FU periods.
j. Evaluation of ongoing treatment-emergent adverse events.
k. See Table 15 for details of hematology tests.
l. See Table 15 for details of serum chemistry tests.
m. Urinalysis: dipstick followed by microscopic examination if abnormal results.
n. 12-lead resting ECG in triplicate.
o. 12-lead ECG to be performed predose and once at 2 to 3 hours postdose.
p. 12-lead ECG to be performed at 2 hours postdose.
q. Tumor imaging by CT or MRI at baseline to document extent of lesions according to RECIST v1.1. Baseline tumor evaluation can be up to 28 days old when treatment starts.
r. Tumor assessments to be done at long-term safety FU (every 6 weeks during Day 31-180 [4 assessments]) and during survival FU (every 13 weeks during Day 181-365 [2 assessments]). Tumor assessment will not be repeated on PTD 180.
s. PK samples will be collected as detailed in Table 9. Sampling schedule may be changed by the SMC based on emerging data. See Section 7.5.1 for details.
t. Predose only.
u. Mandatory archival tumor materials sampled before start of the treatment (most recent materials available). If no archival tumor material is available a fresh biopsy must be taken.

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x. Can be followed up via phone call every 3 months.
y. Subjects treated in the tablet testing cohorts of Phase Ia Arm A will receive the tablet on FD 1-5 and FD 7-10 and a respective single dose strength of the capsule formulation on FD 6.

z. If FD6 is NOT on a Monday then it must be scheduled to take place on the Monday closest to FD6 as wash-out over the weekend is required.
aa. PTD 210 and 312 will consist of phone calls to evaluate long term RT toxicity. No other assessments will be performed at these visits.

**Table 3 Schedule of Assessments – First 3 Subjects in Phase Ib (Arm A; NSCLC Cohort)**

| Trial Periods | Screening | DLT Evaluation Period | | | | | | Mid-term Safety FU | Long-term Safety FU/ EOT[a] | Survival FU |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Treatment Period (M3814 + RT) | | | | | DLT Period/Short-term Safety FU | | | |
| **Trial Days** | **Day -21 to Day -1** | **FD 1 to FD 33** | | | | | **PTD 1 to 37** | **PTD 1 to 90** | **PTD 31 to 365** | **-** |
| **M3814 RT 2 Gy x 33 (5 F/W)[b]** | | **X X** | | | | | | | | |
| **Visit Days** | **-21 to -1** | **FD 1** | **FD 2** | **FD 6** | **FD 10[c]** | **FD 16, 21, 26 and 33/ETT[d]** | **PTD 8, 15, 22, 37[e]** | **PTD 84** | **PTD 42, 126, 168, 180, 210[x], 270, 312[x], and 365** | **-** |
| **Visit Window (days)** | **-** | **-** | **-** | **-** | **-** | **-** | **±2** | **±7** | **±7** | **-** |
| Signed informed consent | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical history | X | | | | | | | | | |
| Serum β-HCG pregnancy test (if applicable) | X | | | | | | PTD 22 only | | | |
| Infection screen (hepatitis B and C), optional HIV test[f] | X | | | | | | | | | |
| Vital signs[g] | X[h] | X | | X | X | X | X | X | X | |
| Physical examination | X | X | | X | X | X | X | X | X[i] | |
| Clinical examination of bleeding | X | X | | X | X | X | X | | | |

| Trial Periods | Screening | DLT Evaluation Period | | | | | | Mid-term Safety FU | Long-term Safety FU/ EOT[a] | Survival FU |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Treatment Period (M3814 + RT) | | | | | DLT Period/Short-term Safety FU | | | |
| **Trial Days** | Day -21 to Day -1 | FD 1 to FD 33 | | | | | PTD 1 to 37 | PTD 1 to 90 | PTD 31 to 365 | - |
| **M3814 RT 2 Gy x 33 (5 F/W)[b]** | | X X | | | | | | | | |
| **Visit Days** | -21 to -1 | FD 1 | FD 2 | FD 6 | FD 10[c] | FD 16, 21, 26 and 33/ETT[d] | PTD 8, 15, 22, 37[e] | PTD 84 | PTD 42, 126, 168, 180, 210[x], 270, 312[x], and 365 | - |
| **Visit Window (days)** | - | - | - | - | - | - | ±2 | ±7 | ±7 | - |
| Esophageal endoscopy (if relevant) | X | | | | | | | | | |
| Evaluation of all tissues in RT area | | | | X | X | X | X | X | X | |
| ECOG PS | X | | | | X | FD 33 only | X | X | X | |
| Adverse event assessment | X | X | | X | X | X | X | X[j] | X[j] | |
| Concomitant medication | X | X | | X | X | X | X | | | |
| Hematology[k] | X | X | | X | X | X | X | | | |
| Serum chemistry and coagulation[l] | X | X | | X | X | X | X | | | |
| Urinalysis (dipstick)[m] | X | | | | X | FD 16 and 33 only | X | | | |
| 12-lead ECG (including QTcF)[n] | X | X[o] | | | X[p] | | | | | |
| Tumor assessment (RECIST)[q, r] | X | | | | | | | X | X | |
| PK blood samples[s] | | X | X[t] | X | X | | | | | |

| Trial Periods | Screening | DLT Evaluation Period | | | | | | Mid-term Safety FU | Long-term Safety FU/ EOT[a] | Survival FU |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Treatment Period (M3814 + RT) | | | | | DLT Period/Short-term Safety FU | | | |
| Trial Days | Day -21 to Day -1 | FD 1 to FD 33 | | | | | PTD 1 to 37 | PTD 1 to 90 | PTD 31 to 365 | - |
| M3814<br>RT 2 Gy x 33 (5 F/W)[b] | | X<br>X | | | | | | | | |
| Visit Days | -21 to -1 | FD 1 | FD 2 | FD 6 | FD 10[c] | FD 16, 21, 26 and 33/ETT[d] | PTD 8, 15, 22, 37[e] | PTD 84 | PTD 42, 126, 168, 180, 210[x], 270, 312[x], and 365 | - |
| Visit Window (days) | - | - | - | - | - | - | ±2 | ±7 | ±7 | - |
| Archival tumor material[u] | X | | | | | | | | | |
| CCI | | | | | | | | | | |
| Survival | | | | | | | | | | X[y] |

AE = adverse event; CT = computed tomography; CCI; DLT= dose limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Trial; ETT = Early Treatment Termination; FD = fraction day; FU = follow-up; F/W = fraction per week; Gy = Gray; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; CCI; CCI; PK = pharmacokinetics; PTD = Post-treatment Day; QTcF = Fridericia-corrected QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiotherapy; SMC = Safety Monitoring Committee.

Note: Fraction Day (FD): days when RT and M3814 is given. Post-treatment Day (PTD): days in the period starting as of end of the treatment period until 1 year later.

a. All subjects will be followed up for survival until 12 months after the last subject has stopped RT/CRT. All subjects will be followed up for response until 12 months after RT is completed, or earlier due to any reason whereby tumor assessments are no longer applicable (e.g., if a new treatment is started, withdrawal of consent). The reason for early discontinuation should be captured in the source document. If EOT occurs before PTD 365, all assessments must be done as planned for PTD 365. After completing the PTD 365 visit, subjects will be followed up for survival via phone call every 3 months, wherever possible.

b. RT to be given 1.5 hours (± 30 minutes) after dosing.
c. If FD10 is on a Friday, PK, PD, safety laboratory, and urinalysis sampling must be done on FD9.
d. FD 33 is the day of the last dose of RT. In case of premature withdrawal during the treatment period, the investigations scheduled for the visit on FD 33 should be performed. In such cases, this visit will be considered the Early Treatment Termination visit.
e. All AEs will be collected from FD1 up to PTD 37 to evaluate the occurrence of DLTs.
f. Hepatitis B and C testing to be performed at Screening unless obtained within 3 months prior to Screening. Screening for HIV will be performed according to local practice and local regulatory guidance.
g. Heart rate, diastolic and systolic blood pressure, body temperature, and body weight. See Section 7.4.4 for details.
h. Height measured at Screening only.
i. Physical exam will report findings in the irradiated area during all FU periods.
j. Evaluation of ongoing treatment-emergent adverse events.
k. See Table 15 for details of hematology tests.
l. See Table 15 for details of serum chemistry tests.
m. Urinalysis: dipstick followed by microscopic examination if abnormal results.
n. 12-lead resting ECG in triplicate.
o. 12-lead ECG to be performed predose and once at 2 to 3 hours postdose.
p. 12-lead ECG to be performed at 2 hours postdose.
q. Tumor imaging by CT or MRI at baseline to document extent of lesions and absence of metastases (M0 stage) according to RECIST v1.1. Baseline tumor evaluation can be up to 28 days old when treatment starts.
r. Tumor assessments to be done at long-term safety FU (every 6 weeks during Day 31-180 [4 assessments] and every 13 weeks during Day 181-365 [2 assessments]). Tumor assessment will not be repeated on PTD 180.
s. PK samples for the first 3 subjects in Phase Ib will follow the sampling for Phase Ia as detailed in Table 9. Sampling schedule may be changed by the SMC based on emerging data. See Section 7.5.1 for details.
t. Predose only.
u. Mandatory archival tumor materials sampled before start of the treatment (most recent materials available).
CCI [redacted]
x. PTD 210 and 312 will consist of phone calls to evaluate long term RT toxicity. No other assessments will be performed at these visits.
y. Can be followed up via phone call every 3 months.

**Table 4 Schedule of Assessments – Phase Ib (Arm A; NSCLC Cohort)**

| Trial Periods | Screening | Treatment Period (M3814 + RT) | | | Short-term Safety FU | Mid-term Safety FU | Long-term Safety FU/ EOT[a] | Survival FU |
|---|---|---|---|---|---|---|---|---|
| **Trial Days** | **Day -21 to Day -1** | **FD 1 to FD 33** | | | **PTD 1 to 30** | **PTD 1 to 90** | **PTD 31 to 365** | **-** |
| **M3814 RT 2 Gy x 33 (5 F/W)[b]** | | **X X** | | | | | | |
| **Visit Days** | **-21 to -1** | **FD 1** | **FD 10[c]** | **FD 6, 16, 21, 26 and 33/ETT[d]** | **PTD 8, 15, 22, 30** | **PTD 84** | **PTD 42, 126, 168, 180, 210[v], 270, 312[v], and 365** | **-** |
| **Visit Window (days)** | **-** | **-** | **-** | **-** | **±2** | **±7** | **±7** | **-** |
| Signed informed consent | X | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | |
| Demography | X | | | | | | | |
| Medical history | X | | | | | | | |
| Serum β-HCG pregnancy test (if applicable) | X | | | | PTD 30 only | | | |
| Infection screen (hepatitis B and C), optional HIV test[e] | X | | | | | | | |
| Vital signs[f] | X[g] | X | X | X | X | | X | |
| Physical examination | X | X | X | X | X | X | X[h] | |
| Clinical examination of bleeding | X | X | X | X | X | | | |
| Esophageal endoscopy (if relevant) | X | | | | | | | |
| Evaluation of all tissues in RT area | | | X | X | X | X | X | |
| ECOG PS | X | - | | FD 33 only | PTD 30 only | X | X | |
| Adverse event assessment | X | X | X | X | X | X[i] | X[i] | |
| Concomitant medication | X | X | X | X | X | | | |

| Trial Periods | Screening | Treatment Period (M3814 + RT) | | | Short-term Safety FU | Mid-term Safety FU | Long-term Safety FU/ EOT[a] | Survival FU |
|---|---|---|---|---|---|---|---|---|
| Trial Days | Day -21 to Day -1 | FD 1 to FD 33 | | | PTD 1 to 30 | PTD 1 to 90 | PTD 31 to 365 | - |
| M3814 RT 2 Gy x 33 (5 F/W)[b] | | X X | | | | | | |
| Visit Days | -21 to -1 | FD 1 | FD 10[c] | FD 6, 16, 21, 26 and 33/ETT[d] | PTD 8, 15, 22, 30 | PTD 84 | PTD 42, 126, 168, 180, 210[v], 270, 312[v], and 365 | - |
| Visit Window (days) | - | - | - | - | ±2 | ±7 | ±7 | - |
| Hematology[j] | X | X | X | X | X | | | |
| Serum chemistry and coagulation[k] | X | X | X | X | X | | | |
| Urinalysis (dipstick)[l] | X | | | FD 16 and 33 only | PTD 30 only | | | |
| 12-lead ECG (including QTcF)[m] | X | X[n] | X[o] | | | | | |
| Tumor assessment (RECIST)[p, q] | X | | | | | X | X | |
| PK blood samples[r] | | X | X | | | | | |
| Archival tumor material[s] | X | | | | | | | |
| CCI [redacted] | | | | | | | | |
| Survival | | | | | | | | X[w] |

CT = computed tomography; CCI [redacted]; DLT= dose limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Trial; ETT = Early Treatment Termination; FD = fraction day; FU = follow-up; F/W= fraction per week; Gy = Gray; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; CCI [redacted]; CCI [redacted]; PK = pharmacokinetics; PTD = Post-treatment Day; QTcF = Fridericia-corrected QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiotherapy; SMC = Safety Monitoring Committee.

Note: Fraction Day (FD): days when RT and M3814 is given. Post-treatment Day (PTD): days in the period starting as of end of the treatment period until 1 year later

a. All subjects will be followed up for survival until 12 months after the last subject has stopped RT/CRT. All subjects will be followed up for response until 12 months after RT is completed, or earlier due to any reason whereby tumor assessments are no longer applicable (e.g., if a new treatment is started, withdrawal of consent). The reason for early discontinuation should be captured in the source document. If EOT occurs before PTD 365, all assessments must be done as planned for PTD 365. After completing the PTD 365 visit, subjects will be followed up for survival via phone call every 3 months, wherever possible.
b. RT to be given 1.5 hours (± 30 minutes) after dosing.
c. If FD10 is on a Friday, PK, PD, and safety laboratory sampling must be done on FD9.
d. FD 33 is the day of the last dose of RT. In case of premature withdrawal during the treatment period, the investigations scheduled for the visit on FD 33 should be performed. In such cases, this visit will be considered the Early Treatment Termination visit.
e. Hepatitis B and C testing to be performed at Screening unless obtained within 3 months prior to Screening. Screening for HIV will be performed according to local practice and local regulatory guidance.
f. Heart rate, diastolic and systolic blood pressure, body temperature, and body weight. See Section 7.4.4 for details.
g. Height measured at Screening only.
h. Physical exam will report findings in the irradiated area during all FU periods.
i. Evaluation of ongoing treatment-emergent adverse events.
j. See Table 15 for details of hematology tests.
k. See Table 15 for details of serum chemistry tests.
l. Urinalysis: dipstick followed by microscopic examination if abnormal results.
m. 12-lead resting ECG in triplicate.
n. 12-lead ECG to be performed predose and once at 2 to 3 hours postdose.
o. 12-lead ECG to be performed at 2 hours postdose.
p. Tumor imaging by CT or MRI at baseline to document extent of lesions and absence of metastases (M0 stage) according to RECIST v1.1. Baseline tumor evaluation can be up to 28 days old when treatment starts.
q. Tumor assessments to be done at long-term safety FU (every 6 weeks during Day 31-180 [4 assessments] and every 13 weeks during Day 181-365 [2 assessments]). Tumor assessment will not be repeated on PTD 180.
r. Sparse PK samples will be collected as detailed in Table 9. These sampling time points might be re-scheduled based on PK results from Phase Ia by the SMC.
s. Mandatory archival tumor materials sampled before start of the treatment (most recent materials available). If no archival material is available then a fresh biopsy should be taken.

CCI [redacted]

v. PTD 210 and 312 will consist of phone calls to evaluate long term RT toxicity. No other assessments will be performed at these visits.
w. Can be followed up via phone call every 3 months.

## Table 5 Schedule of Assessments – Phase Ia (Arm B; SCCHN Cohort)

| Trial Periods | Screening | DLT Evaluation Period | | | | | | Mid-term Safety FU | Long-term Safety FU/ EOT[a] | Survival FU |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Treatment Period (M3814 + RT + Cisplatin) | | | | | DLT Period/ Short-term Safety FU | | | |
| **Trial Days** | Day -21 to Day -1 | FD 1 to FD 33-35 | | | | | PTD 1 to 35 | PTD 1 to 90 | PTD 31 to 365 | - |
| **M3814<br>RT 2 Gy x 33-35 (5 F/W)[b]<br>Cisplatin** | - | X<br>X<br>100 mg/m$^2$ twice (FD 1, 31) or 40 mg/m$^2$ weekly | | | | | - | - | | |
| **Visit Days** | -21 to -1 | FD 1 | FD 2 | FD 6 | FD 10[c] | FD 16, 21, 26, 31 and last FD/ETT[d] | PTD 7, 14, 21, 28, 35[e] | PTD 84 | PTD 42, 126, 168, 180, 210[z], 270, 312[z], and 365 | - |
| **Visit Window (days)** | - | - | - | - | - | - | ±2 | ±7 | ±7 | - |
| Signed informed consent | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical history | X | | | | | | | | | |
| Serum β-HCG pregnancy test (if applicable) | X | | | | | | PTD 28 only | | | |
| Infection screen (hepatitis B and C), optional HIV test[f] | X | | | | | | | | | |
| HPV status in tumor[g] | X | | | | | | | | | |
| Audiogram[h] | X | | | | | | | | | |
| Vital signs[i] | X[j] | X | | X | X | X | X | X | X | |
| Physical examination | X | X | | X | X | X | X | X | X[k] | |
| Clinical examination of bleeding | X | X | | X | X | X | X | | | |

| Trial Periods | Screening | DLT Evaluation Period | | | | | | Mid-term Safety FU | Long-term Safety FU/ EOT[a] | Survival FU |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Treatment Period (M3814 + RT + Cisplatin) | | | | | DLT Period/ Short-term Safety FU | | | |
| **Trial Days** | Day -21 to Day -1 | FD 1 to FD 33-35 | | | | | PTD 1 to 35 | PTD 1 to 90 | PTD 31 to 365 | - |
| **M3814<br>RT 2 Gy x 33-35 (5 F/W)[b]<br>Cisplatin** | - | X<br>X<br>100 mg/m² twice (FD 1, 31) or 40 mg/m² weekly | | | | | - | - | | |
| **Visit Days** | -21 to -1 | FD 1 | FD 2 | FD 6 | FD 10[c] | FD 16, 21, 26, 31 and last FD/ETT[d] | PTD 7, 14, 21, 28, 35[e] | PTD 84 | PTD 42, 126, 168, 180, 210[z], 270, 312[z], and 365 | - |
| **Visit Window (days)** | - | - | - | - | - | - | ±2 | ±7 | ±7 | - |
| Esophageal endoscopy (if relevant) | X | | | | | | | | | |
| Evaluation of all tissues in RT area | | | | X | X | X | X | X | X | |
| ECOG PS | X | | | | X | Last FD only | X | X | X | |
| Adverse event assessment | X | X | | X | X | X | X | X[l] | X[l] | |
| Concomitant medication | X | X | | X | X | X | X | | | |
| Hematology[m] | X | X | | X | X | X | X | | | |
| Serum chemistry and coagulation[n] | X | X | | X | X | X | X | | | |
| Urinalysis (dipstick)[o] | X | | | | X | FD 16 and last FD only | X | | | |
| 12-lead ECG (including QTcF)[p] | X | X[q] | | | X[r] | X[r] | | X[r] | X[r] | |
| Tumor assessment (RECIST)[s, t] | X | | | | | | | X | X | |
| PK blood samples[u] | | X | X[v] | X | X | | | | | |
| Archival tumor material[w] | X | | | | | | | | | |
| CCI [redacted] | | | | | | | | | | |

| Trial Periods | Screening | DLT Evaluation Period | | | | | | Mid-term Safety FU | Long-term Safety FU/ EOT[a] | Survival FU |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Treatment Period (M3814 + RT + Cisplatin) | | | | | DLT Period/ Short-term Safety FU | | | |
| Trial Days | Day -21 to Day -1 | FD 1 to FD 33-35 | | | | | PTD 1 to 35 | PTD 1 to 90 | PTD 31 to 365 | - |
| M3814<br>RT 2 Gy x 33-35 (5 F/W)[b]<br>Cisplatin | - | X<br>X<br>100 mg/m² twice (FD 1, 31) or 40 mg/m² weekly | | | | | - | - | | |
| Visit Days | -21 to -1 | FD 1 | FD 2 | FD 6 | FD 10[c] | FD 16, 21, 26, 31 and last FD/ETT[d] | PTD 7, 14, 21, 28, 35[e] | PTD 84 | PTD 42, 126, 168, 180, 210[z], 270, 312[z], and 365 | - |
| Visit Window (days) | - | - | - | - | - | - | ±2 | ±7 | ±7 | - |
| CCI [redacted] | | | | | | | | | | |
| Survival | | | | | | | | | | X[aa] |

AE = adverse event; CT = computed tomography; CCI [redacted] DLT = dose limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Trial; ETT = Early Treatment Termination; FD = fraction day; FU = follow-up; F/W = fraction per week; Gy = Gray; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; HPV = human papillomavirus; MRI = magnetic resonance imaging; CCI [redacted]; CCI [redacted]; PK = pharmacokinetics; PTD = Post-treatment Day; QTcF = Fridericia-corrected QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiotherapy; SMC = Safety Monitoring Committee.

Note: Fraction Day (FD): days when RT and M3814 is given (plus cisplatin on FDs as specified above). Post-treatment Day (PTD): days in the period starting as of end of the treatment period until 1 year later.

a. All subjects will be followed up for survival until 12 months after the last subject has stopped RT/CRT. All subjects will be followed up for response until 12 months after RT is completed, or earlier due to any reason whereby tumor assessments are no longer applicable (e.g., if a new treatment is started, withdrawal of consent). The reason for early discontinuation should be captured in the source document. If EOT occurs before PTD 365, all assessments must be done as planned for PTD 365. After completing the PTD 365 visit, subjects will be followed up for survival via phone call every 3 months, wherever possible.
b. RT to be given 1.5 hours (± 30 minutes) after dosing.
c. If FD10 is on a Friday, PK, PD, safety laboratory, and urinalysis sampling must be done on FD9.
d. FD 33-35 is the day of the last dose of RT. In case of premature withdrawal during the treatment period, the investigations scheduled for the visit on the last FD should be performed. In such cases, this visit will be considered the Early Treatment Termination visit.
e. All AEs will be collected from FD1 up to PTD 33-35 to evaluate the occurrence of DLTs.

f. Hepatitis B and C testing to be performed at Screening unless obtained within 3 months prior to Screening. Screening for HIV will be performed according to local practice and local regulatory guidance.
g. Immunohistochemistry in tumor material.
h. As needed according to local guidelines.
i. Heart rate, diastolic and systolic blood pressure, body temperature, and body weight. See Section 7.4.4 for details.
j. Height measured at Screening only.
k. Physical exam will report findings in the irradiated area during all FU periods.
l. Evaluation of ongoing treatment-emergent adverse events.
m. See Table 15 for details of hematology tests.
n. See Table 15 for details of serum chemistry tests.
o. Urinalysis: dipstick followed by microscopic examination if abnormal results.
p. 12-lead resting ECG in triplicate.
q. 12-lead ECG to be performed predose and once at 2 to 3 hours postdose.
r. 12-lead ECG to be performed at 2 hours postdose.
s. Tumor imaging by CT or MRI at baseline to document extent of lesions and absence of metastases (M0 stage) according to RECIST v1.1. Baseline tumor evaluation can be up to 28 days old when treatment starts.
t. Tumor assessments to be done at long-term safety FU (every 6 weeks during Day 31-180 [4 assessments] and every 13 weeks during Day 181-365 [2 assessments]). Tumor assessment will not be repeated on PTD 180.
u. PK samples will follow the sampling for Phase Ia as detailed in Table 9. Sampling schedule may be changed by the SMC based on emerging data. See Section 7.5.1 for details.
v. Predose only.
w. Mandatory archival tumor materials sampled before start of the treatment (most recent materials available).

CCI [redacted]

z. PTD 210 and 312 will consist of phone calls to evaluate long term RT toxicity. No other assessments will be performed at these visits.
aa. Can be followed up via phone call every 3 months.

## Table 6 Schedule of Assessments – Phase Ib (Arm B; SCCHN Cohort)

| Trial Periods | Screening | Treatment Period (M3814 + RT + Cisplatin) | | | Short-term Safety FU | Mid-term Safety FU | Long-term Safety FU/ EOT[a] | Survival FU |
|---|---|---|---|---|---|---|---|---|
| **Trial Days** | **Day -21 to Day -1** | **FD 1 to FD 33-35** | | | **PTD 1 to 30** | **PTD 1 to 90** | **PTD 31 to 365** | **-** |
| **M3814<br>RT 2 Gy x 33-35 (5 F/W)[b]<br>Cisplatin** | **-** | **X<br>X<br>100 mg/m² twice (FD 1, 31) or 40 mg/m² weekly** | | | **-** | **-** | **-** | **-** |
| **Visit Days** | **-21 to -1** | **FD 1** | **FD 10[c]** | **FD 6, 16, 21, 26, 31 and last FD/ETT[d]** | **PTD 8, 15, 22, 30** | **PTD 84** | **PTD 42, 126, 168, 180, 210[x], 270, 312[x], and 365** | **-** |
| **Visit Window (days)** | **-** | **-** | **-** | **-** | **±2** | **±7** | **±7** | **-** |
| Signed informed consent | X | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | |
| Demography | X | | | | | | | |
| Medical history | X | | | | | | | |
| Serum β-HCG pregnancy test (if applicable) | X | | | | PTD 30 only | | | |
| Infection screen (hepatitis B and C), optional HIV test[e] | X | | | | | | | |
| HPV status in tumor[f] | X | | | | | | | |
| Audiogram[g] | X | | | | | | | |
| Vital signs[h] | X[i] | X | X | X | X | | X | |
| Physical examination | X | X | X | X | X | X | X[i] | |
| Clinical examination of bleeding | X | X | X | X | X | | | |
| Esophageal endoscopy (if relevant) | X | | | | | | | |
| Evaluation of all tissues in RT area | | | X | X | X | X | X | |

| Trial Periods | Screening | Treatment Period (M3814 + RT + Cisplatin) | | | Short-term Safety FU | Mid-term Safety FU | Long-term Safety FU/ EOT[a] | Survival FU |
|---|---|---|---|---|---|---|---|---|
| Trial Days | Day -21 to Day -1 | FD 1 to FD 33-35 | | | PTD 1 to 30 | PTD 1 to 90 | PTD 31 to 365 | - |
| M3814<br>RT 2 Gy x 33-35 (5 F/W)[b]<br>Cisplatin | - | X<br>X<br>100 mg/m² twice (FD 1, 31) or 40 mg/m² weekly | | | - | - | - | - |
| Visit Days | -21 to -1 | FD 1 | FD 10[c] | FD 6, 16, 21, 26, 31 and last FD/ETT[d] | PTD 8, 15, 22, 30 | PTD 84 | PTD 42, 126, 168, 180, 210[x], 270, 312[x], and 365 | - |
| Visit Window (days) | - | - | - | - | ±2 | ±7 | ±7 | - |
| ECOG PS | X | - | | Last FD only | PTD 30 only | X | X | |
| Adverse event assessment | X | X | X | X | X | X[k] | X[k] | |
| Concomitant medication | X | X | X | X | X | | | |
| Hematology[l] | X | X | X | X | X | | | |
| Serum chemistry and coagulation[m] | X | X | X | X | X | | | |
| Urinalysis (dipstick)[n] | X | | | FD 16 and last FD only | PTD 30 only | | | |
| 12-lead ECG (including QTcF)[o] | X | X[p] | X[q] | X[q] | | X[q] | X[q] | |
| Tumor assessment (RECIST)[r, s] | X | | | | | X | X | |
| PK blood samples[t] | | X | X | | | | | |
| Archival tumor material[u] | X | | | | | | | |
| CCI [redacted] | | | | | | | | |
| Survival | | | | | | | | X[y] |

CT = computed tomography; ctDNA = circulating tumor DNA; DLT = dose limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Trial; ETT = Early Treatment Termination; FD = fraction day; FU = follow-up; F/W = fraction per week; Gy = Gray; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; HPV = human papillomavirus; MRI = magnetic resonance imaging; PD = pharmacodynamics; PGx = pharmacogenetics; PK = pharmacokinetics; PTD = Post-treatment Day; QTcF = Fridericia-corrected QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiotherapy; SMC = Safety Monitoring Committee.

Note: Fraction Day (FD): days when RT and M3814 is given (plus cisplatin on FDs as specified above). Post-treatment Day (PTD): days in the period starting as of end of the treatment period until 1 year later.

a. All subjects will be followed up for survival until 12 months after the last subject has stopped RT/CRT. All subjects will be followed up for response until 12 months after RT is completed, or earlier due to any reason whereby tumor assessments are no longer applicable (e.g., if a new treatment is started, withdrawal of consent). The reason for early discontinuation should be captured in the source document. If EOT occurs before PTD 365, all assessments must be done as planned for PTD 365. After completing the PTD 365 visit, subjects will be followed up for survival via phone call every 3 months, wherever possible.
b. RT to be given 1.5 hours (± 30 minutes) after dosing.
c. If FD10 is on a Friday, PK, PD, and safety laboratory sampling must be done on FD9.
d. FD 33-35 is the day of the last dose of RT. In case of premature withdrawal during the treatment period, the investigations scheduled for the visit on the last FD should be performed. In such cases, this visit will be considered the Early Treatment Termination visit.
e. Hepatitis B and C testing to be performed at Screening unless obtained within 3 months prior to Screening. Screening for HIV will be performed according to local practice and local regulatory guidance.
f. Immunohistochemistry in tumor material.
g. As need according to local guidelines.
h. Heart rate, diastolic and systolic blood pressure, body temperature, and body weight. See Section 7.4.4 for details.
i. Height measured at Screening only.
j. Physical exam will report findings in the irradiated area during all FU periods.
k. Evaluation of ongoing treatment-emergent adverse events.
l. See Table 15 for details of hematology tests.
m. See Table 15 for details of serum chemistry tests.
n. Urinalysis: dipstick followed by microscopic examination if abnormal results.
o. 12-lead resting ECG in triplicate.
p. 12-lead ECG to be performed predose and once at 2 to 3 hours postdose.
q. 12-lead ECG to be performed at 2 hours postdose.
r. Tumor imaging by CT or MRI at baseline to document extent of lesions and absence of metastases (M0 stage) according to RECIST v1.1. Baseline tumor evaluation can be up to 28 days old when treatment starts.
s. Tumor assessments to be done at long-term safety FU (every 6 weeks during Day 31-180 [4 assessments] and every 13 weeks during Day 181-365 [2 assessments]). Tumor assessment will not be repeated on PTD 180.
t. Sparse PK samples will be collected as detailed in Table 9. These sampling time points might be re-scheduled based on PK results from Phase Ia by the SMC.
u. Mandatory archival tumor materials sampled before start of the treatment (most recent materials available). If no archival material is available then a fresh biopsy should be taken.

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w. Predose whole blood and plasma sampling for PGx.
x. PTD 210 and 312 will consist of phone calls to evaluate long term RT toxicity. No other assessments will be performed at these visits.
y. Can be followed up via phone call every 3 months.

## Table 7 Schedule of Assessments – Ancillary Clinical Proof-of-Principle Part

| Trial Periods | Screening | Treatment Duration | | FU | Safety Follow up and End of Trial |
|---|---|---|---|---|---|
| **Trial Days** | **Day -21 to -1** | **1** | **2** | **3 to 10** | **11 to 32** |
| **M3814** | - | **-** | **X** | - | - |
| **RT: 10-25 Gy[a]** | | **Lesion 1** | **Lesion 2** | | |
| **Trial Visit Day** | **–21 to –1** | **1[b]** | **2** | **10** | **32** |
| **Visit window (days)** | **-** | **-** | **-** | **±1** | **±2** |
| Signed informed consent | X | | | | |
| Inclusion/exclusion criteria | X | | | | |
| Demography | X | | | | |
| Medical history | X | | | | |
| Serum pregnancy test (if applicable) | X | | | | |
| Infection screen (hepatitis B and C), optional HIV test[c] | X | | | | |
| Vital signs[d] | X[e] | X[f] | X[f] | X | |
| Physical examination | X | | | | |
| Evaluation of all tissues in RT area | X | | X | X | X |
| ECOG PS | X | | | | |
| Adverse event assessment | X | X | X | X | X[g] |
| Concomitant medication | X | X | X | X | |
| Hematology[h] | X | | | X | X |
| Serum chemistry and coagulation[i] | X | | | X | X |
| Urinalysis (dipstick)[j] | X | | | | |

| Trial Periods | Screening | Treatment Duration | | FU | Safety Follow up and End of Trial |
|---|---|---|---|---|---|
| Trial Days | Day -21 to -1 | 1 | 2 | 3 to 10 | 11 to 32 |
| M3814 | - | - | X | - | - |
| RT: 10-25 Gy[a] | | Lesion 1 | Lesion 2 | | |
| Trial Visit Day | –21 to –1 | 1[b] | 2 | 10 | 32 |
| Visit window (days) | - | - | - | ±1 | ±2 |
| 12-lead ECG (including QTcF) | X | | | | |
| CCI | | | | | |
| PK blood sample | | | X[m] | | |
| CCI | | | | | |
| Local tumor assessment (RECIST)[o, p] | X | | | X | |

ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FU = follow-up; F/W= fraction per week; Gy = Gray; HIV = human immunodeficiency virus; L1 = Lesion 1; L2 = Lesion 2; PD = pharmacodynamics; PK = pharmacokinetics; QTcF = Fridericia-corrected QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiotherapy.

a. To be given 1.5 hours (± 30 minutes) after dosing.
b. For logistical reasons (handling and sending materials), Day 1 must be on a Wednesday or earlier.
c. Hepatitis B and C testing to be performed at Screening unless obtained within 3 months prior to Screening. Screening for HIV will be performed according to local practice and local regulatory guidance.
d. Heart rate, diastolic and systolic blood pressure, body temperature, and body weight.
e. Height measured at Screening only.
f. Predose vital signs.
g. Local tolerability only.
h. See Table 15 for details of hematology tests.
i. See Table 15 for details of serum chemistry tests.
j. Urinalysis: dipstick followed by microscopic examination if abnormal results.

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m. PK samples will be collected as described in Table 9. Sampling schedule may be changed in the course of the trial.

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o. Local tumor assessment (in irradiated lesions) by clinical exam or imaging according to RECIST v1.1. Baseline tumor evaluation can be up to 21 days old when treatment starts.
p. Only applicable for additional cohorts with M3814 CCI [redacted] formulation.

**Table 8 Radiotherapy (Alone) and M3814 + RT Schedule for the Ancillary Clinical Proof-of-Principle (cPoP) Part of the Trial**

| | | Day 1 (baseline)[a] | Day 1 | Day 2 |
|---|---|---|---|---|
| **Lesion 1** | **Biopsy** | B1 | B3[b] | -- |
| | **RT[c]** | -- | + | -- |
| | **M3814** | -- | - | -- |
| **Lesion 2** | **Biopsy** | B2 | -- | B4[b] |
| | **RT[c]** | -- | -- | + |
| | **M3814** | -- | -- | + |

RT = radiotherapy.

a. Baseline biopsy to be taken any time prior to RT for both lesions (Screening to Day 1).

b. Core biopsy needs to be performed 2 to 4 hours after RT. Detailed time schedule and sample collection procedures will be described in the laboratory manual.

c. Radiotherapy will be given as a single high dose of RT (10-25 Gy). The dose of M3814 should be administered 1.5 hours (± 30 minutes) before radiotherapy.

**Table 9** **Pharmacokinetic and [CCI] Sampling Schedule of M3814 during Phase Ia, Phase Ib, and the Ancillary cPoP Part of the Trial**

| | Time points<br>Volume of blood required per time point[a] | Phase Ia<br>PK[c]<br>2 mL | Phase Ib[b]<br>PK[c]<br>2 mL | Ancillary cPoP<br>PK[c]<br>2 mL |
|---|---|---|---|---|
| **FD 1** | Predose | X | X | |
| | H 0.5 | X | X | |
| | H 1.0 | X | | |
| RT | 1.5 hours (± 30 minutes) after dosing | 3 Gy x 10; 5 2 Gy x 33-35; | 2 Gy x 33; 5 2 Gy x 33-35; 5 | 10-25 |
| | H 2.0 | X | X | |
| | H 4.0 | X | X | |
| | H 6.0 | X | X | |
| **FD 2** | Predose[d] | X | | X |
| | H 0.5 | | | X |
| | H 1.0 | | | X |
| RT | 1.5 hours (± 30 minutes) after dosing | 3 Gy x 10; 5 2 Gy x 33-35; | 2 Gy x 33; 5 2 Gy x 33-35; 5 | 10-25 |
| | H 2.0 | | | X |
| | H 4.0 | | | X |
| **FD 6** | Predose[d] | X | | |
| | H 0.5[g] | X | | |
| | H 1.0[g] | X | | |
| RT | 1.5 hours (± 30 minutes) after dosing | 3 Gy x 10; 5 2 Gy x 33-35; | 2 Gy x 33; 5 2 Gy x 33-35; 5 | |
| | H 2.0[g] | X | | |
| | H 4.0[g] | X | | |
| | H 6.0[g] | X | | |
| **FD 7[g]** | Predose[d] | X | | |
| **FD 10[f]** | Predose[d] | X | X | |
| | H 0.5 | X | X | |
| | H 1.0 | X | | |
| RT | 1.5 hours (± 30 minutes) after dosing | 3 Gy x 10; 5 2 Gy x 33-35; | 2 Gy x 33; 5 2 Gy x 33-35; 5 | |
| | H 2.0 | X | X | |
| | H 4.0 | X | X | |

cPoP = clinical proof-of-principle; FD = fraction day; F/W= fraction per week; Gy = Gray; NSCLC = non-small cell lung cancer; [CCI]; PK = pharmacokinetic; RT = radiotherapy; SCCHN = squamous cell carcinoma head and neck; SMC = Safety Monitoring Committee.

a Pharmacokinetic sampling should be performed within ± 15 minutes of the first 30 minute postdose sample collections, and within ± 30 minutes for subsequent sampling at each sampling day. The predose sample should be taken within 1 hour before dosing at each sampling day.

b PK and CCI sampling for the first 3 subjects in Phase Ib (NSCLC expansion cohort) will follow the same schedule as for Phase Ia, as shown in this table.

CCI

d For the purpose of PK parameter calculations, the predose value will also serve as an estimate for the 24-hour postdose concentrations of the previous FD.

e The blood sample closest in time to the biopsy should be collected as close as possible to the time of the biopsy.

f If FD 10 is on a Friday, PK and CCI sampling must be done on FD 9.

g Only for patients treated in the tablet testing cohorts in Phase Ia Arm A.

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## 2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany (in all countries except the United States of America [USA]) and EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), 45A Middlesex Turnpike, Billerica, MA 01821, USA, for sites in the USA.

The trial will appear in the following clinical trial registries: EudraCT and ClinicalTrials.gov.

### 2.1 Investigational Sites

The trial will be conducted at approximately 12 sites in approximately 4 countries in Europe and approximately 8 sites in the USA. Investigators will be radiotherapist/oncologists practicing in these countries. Additional details are included in Appendix C.

### 2.2 Coordinating Investigator

The Coordinating Investigator PPD represents all Investigators for decisions and discussions regarding this trial, consistent with the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guidance (1996), hereafter referred to as ICH GCP. The

Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and sign off of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix A.

## 2.3 Key Parties and Service Providers

This trial will be outsourced, and the Sponsor has engaged PPD (previously known as PPD and PPD), a Contract Research Organization (CRO) to oversee the clinical conduct of this trial.

The other key parties involved in the conduct of the trial are listed in Table 10. The Sponsor and CRO may also engage other third-party providers as necessary.

**Table 10 Trial Administrative Structure**

| | |
|---|---|
| **Project Management:**<br>PPD Europe<br>PPD USA | **Manufacture of Drug Product:**<br>Merck KGaA<br>Darmstadt, Germany (capsules)<br>PPD capsules)<br>PPD<br>(tablets) |
| **Trial Monitoring:**<br>PPD Europe<br>PPD USA | **Trial Drug Packaging and Labeling (PiC formulation):**<br>PPD<br>PPD PPD |
| **Drug Safety Reporting:**<br>PPD Europe<br>PPD USA | **Trial Drug Packaging and Labeling CCI tablet formulation):**<br>PPD<br>PPD |
| **Biostatistics:**<br>PPD Europe<br>PPD USA | **Biomarker Analyses:**<br>Under responsibility of Merck KGaA<br>Darmstadt, Germany |
| **Data Management:**<br>PPD Europe<br>PPD USA | **Pharmacokinetic/Immunogenicity Analyses**<br>PPD Europe<br>PPD USA |

PiC = powder-in-capsule; CCI = CCI

## 2.4 Trial Coordination/Monitoring

The Sponsor and/or its designee will be responsible for the clinical trial documents to be submitted to regulatory authorities, the conduct of the clinical trial, the central laboratory including coordination and distribution of laboratory supplies, drug supply and distribution, data management, statistical analysis and clinical trial reporting. Further details will be provided in a separate document and updated as necessary. Clinical quality assurance will be performed under the responsibility of the Development Quality Assurance department at Merck.

## 2.5 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will review all available the safety data on a regular basis during all parts of the trial. The SMC consists of members from the Sponsor (including the Medical Responsible, the Drug Safety Product Lead, and the Statistician) and Investigators. The SMC will decide on dose limiting toxicities (DLTs) relevant for the treatment and will decide by consensus on dose escalation, dose de-escalation, extension at same dose level is missing, or suspension of enrollment based on safety and PK data. Once PK data becomes available for the tablet, the SMC will also decide on which formulation to move forward with.

The SMC defines the recommended Phase II dose (RP2D) based upon the proposed dose of the Bayesian escalation model and/or available PK data in subjects. The PK and PD sampling times may be modified following review of available safety and PK data by the SMC.

During the expansion cohorts in Phase Ib, the SMC will evaluate safety data from each cohort after 15 subjects have been treated and followed for at least 30 days. The SMC will evaluate the tolerability of each cohort separately, i.e., evaluate the safety data for the Arm A expansion cohort and decide if modifications are required to the dose of M3814 (also referred to as MSC2490484A) or if other measures are to be implemented for subjects treated in this cohort. Similar evaluations will be performed for subjects treated in the Arm B expansion cohort.

Once all subjects in Phase Ib (both arms) have completed their treatment and been followed for at least 3 months, the SMC will evaluate all safety data from the trial.

The ancillary clinical proof-of-principle (cPoP) part of the trial will initially be conducted with the capsule; however, additional cohorts of M3814 ([CCI] [CCI] formulation) may be introduced. The starting dose and subsequent dose levels of M3814 ([CCI] formulation) will be defined by the SMC based on PK and safety data generated in ongoing clinical studies evaluating the safety, tolerability, PK, and PD of M3814 ([CCI] formulation).The specific working procedures of the SMC will be described in the SMC charter.

# 3 Background Information

Physical or chemical agents that generate breaks in DNA are the most widely used classes of cancer therapeutics today. Inducing multiple breaks in cellular DNA, including double-strand breaks (DSBs), which are the most difficult to repair, may lead to induction of cell cycle arrest and/or apoptosis and ultimately cell death if left unrepaired.

Deoxyribonucleic acid-dependent protein kinase (DNA-PK), a member of the phosphoinositol-3 kinase (PI3K) family, is expressed in all tissues and frequently overexpressed in many cancers. Levels of DNA-PK rise after radiotherapy (RT) in response to the increase in DNA DSBs. DNA-PK activity is critical for nonhomologous end joining, a major DNA DSB repair system. Furthermore, DNA-PK inhibition has been shown to increase DSB after therapeutic doses of radiation and could potentiate its therapeutic effect.

The Investigational Medicinal Product (IMP) in this trial, M3814, is a potent and selective inhibitor of DNA-PK, with a 50% inhibitory concentration of 0.6 nM at 5 µM adenosine triphosphate.

M3814 also targets PI3K, specifically the delta isoform, at a concentration 155-fold higher than that needed to obtain an inhibition of DNA-PK. The concentrations necessary to inhibit the various other PI3K isoforms are 400-500 times higher than that needed to inhibit DNA-PK. One additional known off-target of interest is affected by M3814, human cyclo-oxygenase, with a 50% inhibitory concentration of 1.7 µM.

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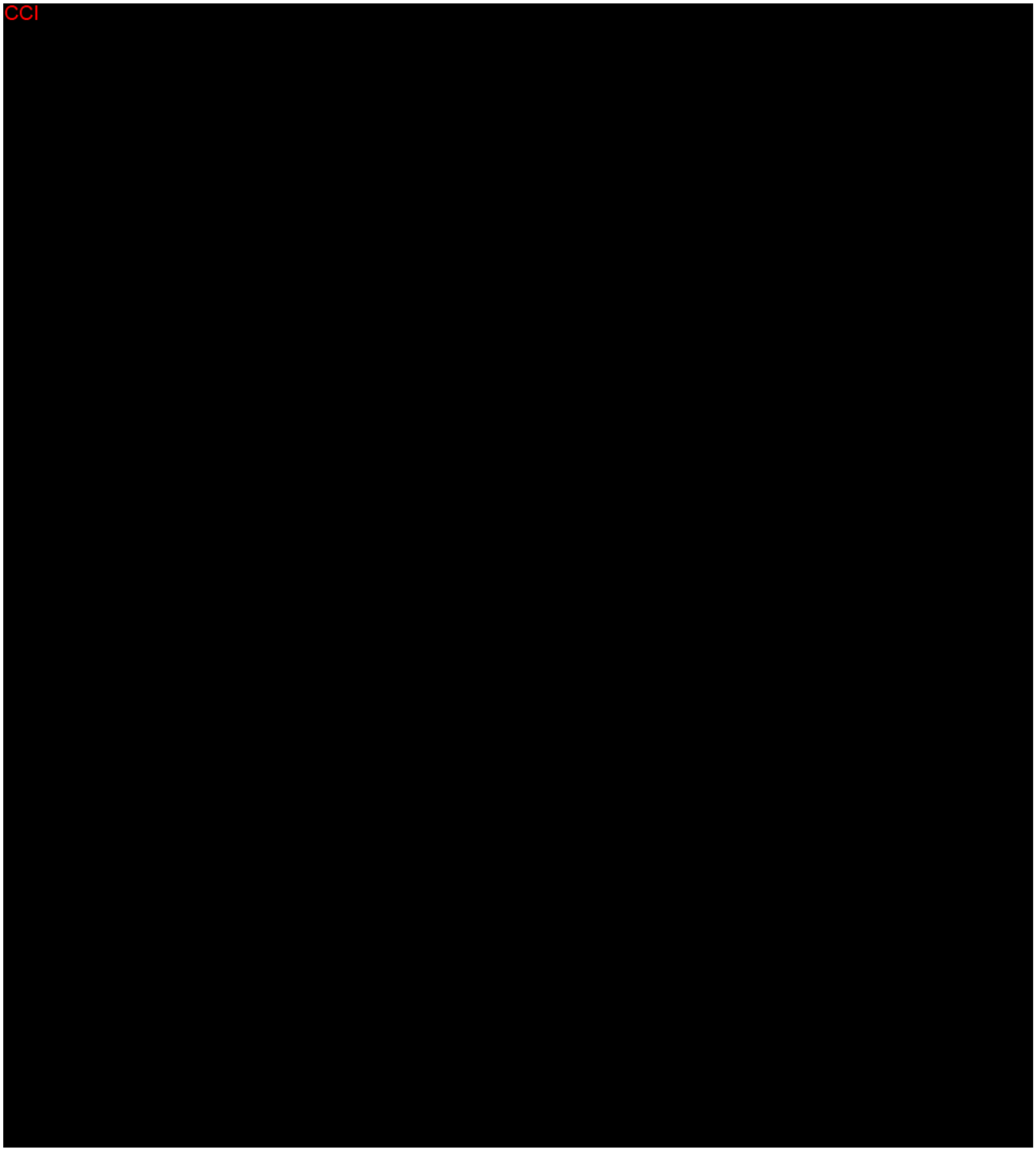

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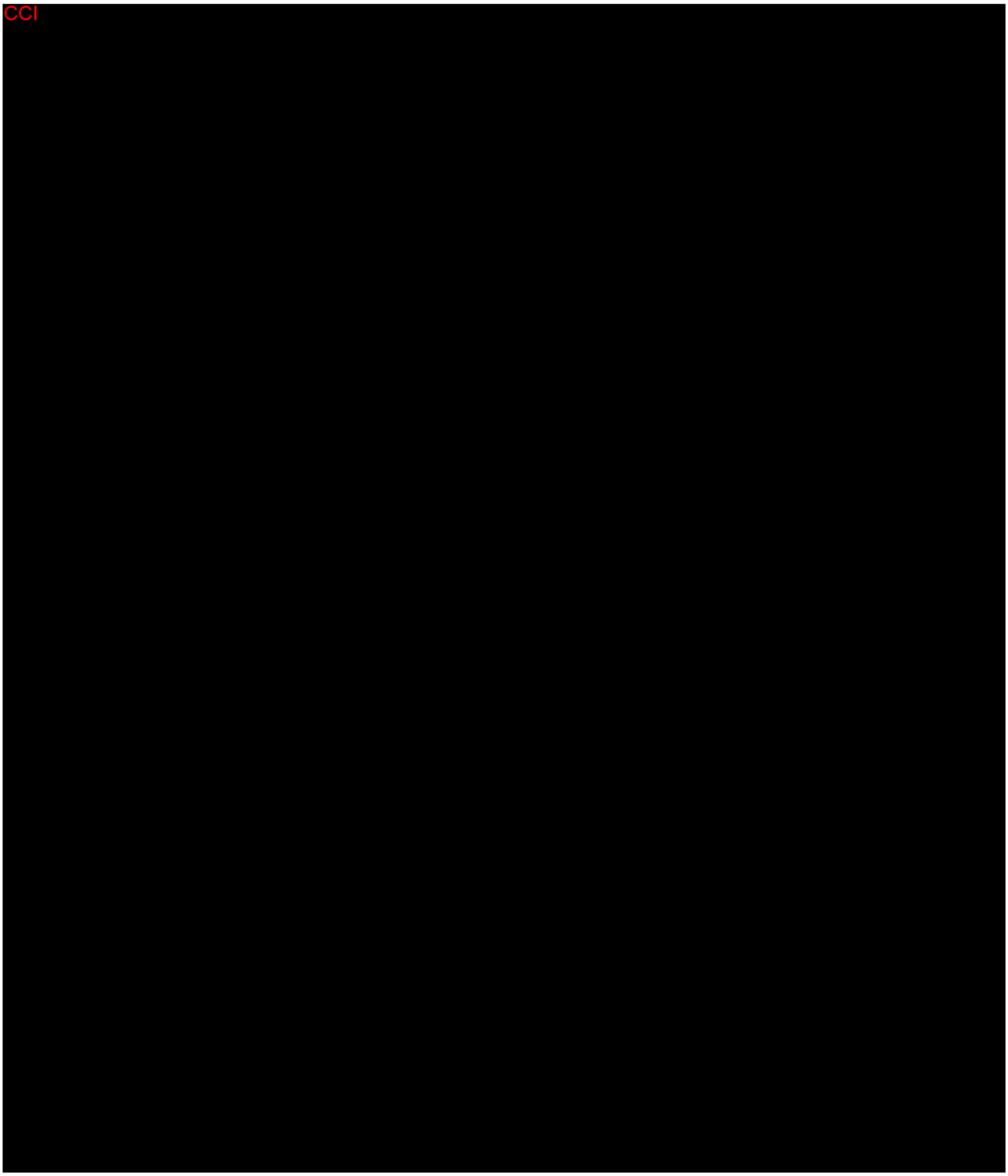

### 3.1.2 Formulation Development

A powder in capsule (PiC) formulation is used in this trial; these capsules are filled with bulk drug substance and do not contain any excipients. However, the production process for the capsules is

not easily sustainable for studies with a high number of subjects. The drug product that is going to be used for Phase II should be a formulation manufactured with acceptable scale-up ability of the pharmaceutical process to easily supply Phase II trials. Therefore, film-coated CCI tablets have been developed and are going to be investigated in this trial.

## 3.2 Trial Population

The trial population in Phase Ia, Arm A, consists of previously treated subjects diagnosed with locally advanced disease (any tumor including lymphomas) localized in the head and neck region or thorax that is not amenable to surgical therapy with an indication for palliative RT (30 Gy in 10 fractions). Phase Ia, Arm B, consists of subjects with treatment-naïve squamous cell carcinoma head and neck (SCCHN) eligible for a course of curatively intended RT (66 to 70 Gy in 33 to 35 fractions) with concurrent cisplatin. In the Phase Ib part, the trial population is treatment-naïve subjects with non-small cell lung cancer (NSCLC) Stage III A/B (not eligible for surgical resection or concurrent chemoradiation) eligible for a course of curatively intended RT (66 Gy in 33 fractions) (Arm A); a further trial population of SCCHN subjects, as specified for Arm B in Phase Ia and using the same chemoradiotherapy (CRT) regimen, will be included (Arm B).

In the ancillary cPoP part of the trial, the trial population is subjects with at least two (sub)cutaneous tumor/metastases of any type (at least 2 cm apart) with an indication for high dose palliative RT (10-25 Gy in one fraction).

## 3.3 Rationale for Trial Design and Justification of Starting Dose

This trial is designed in two sequential parts, and includes one ancillary cPoP part that will run in parallel with the Phase Ia/Ib core trial. Thus, the overall trial has 5 main parts (Figure 1). Phase Ia Arm A will evaluate the safety and tolerability of M3814 in combination with fractionated palliative RT in all-comers with locally advanced tumors or metastases localized in the head and neck region or thorax. Phase Ia Arm B will evaluate the safety and tolerability of M3814 in combination with fractionated curatively intended RT in combination with concurrent cisplatin in subjects with treatment-naïve local/locally advanced SCCHN. The Phase Ib part will evaluate the safety and overall response of M3814 in combination with fractionated curatively intended RT in subjects with Stage III A/B NSCLC and the safety and overall response of M3814 in combination with fractionated curatively intended RT with concurrent cisplatin in subjects with local/locally advanced SCCHN. The ancillary cPoP part of the trial will be conducted in parallel with the Phase Ia/Ib core trial to explore the PD effect of M3814 in combination with RT on target engagement in tumor tissue.

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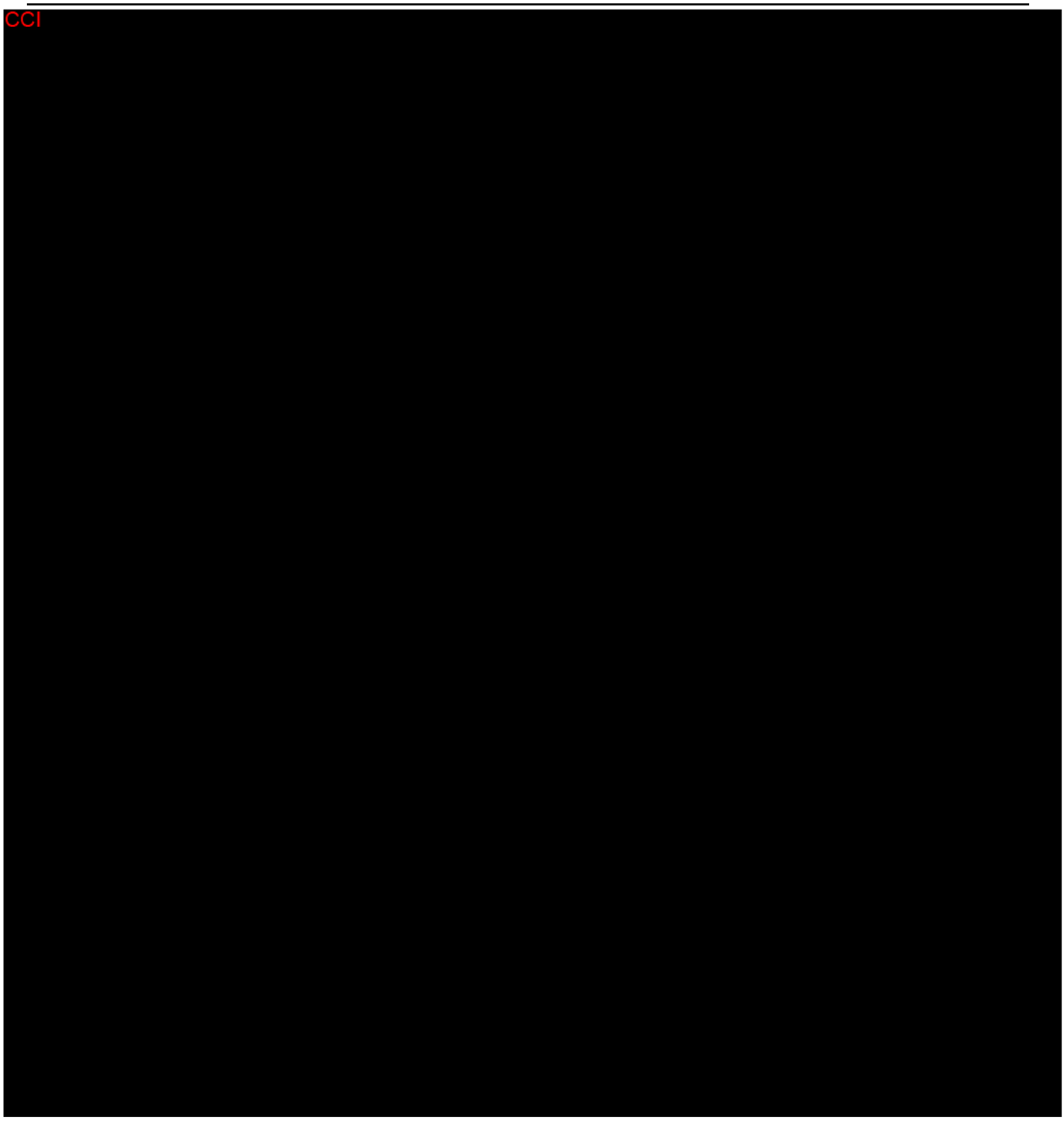

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CCI [redacted]

## 3.4 Rationale for Radiotherapy Dose

The RT doses proposed for the Phase Ia (Arm A: 3 Gy x 10; 5 fractions per week [F/W] and Arm B: 2 Gy x 33 to 35; 5 F/W) and Phase Ib (2 Gy x 33; 5 F/W [NSCLC] and 2 Gy x 33 to 35; 5 F/W [SCCHN]) are Standard of Care (SoC) for palliative and curative intended radiotherapy in the specified areas of the body. In the ancillary cPoP part of the trial (single dose 10-25 Gy) the lower limit of 10 Gy is set as this is the threshold that needs to be given before we can detect the pharmacodynamics signal. The range of 10 to 25 Gy is also the SoC when high dose radiotherapy is given as a single shot.

## 3.5 Rationale for Cisplatin Dose

The dose of cisplatin proposed for Phase Ia, Arm B and Phase Ib, expansion cohort for Arm B (SCCHN) is 100 mg/m$^2$ given twice (on FD 1 and FD 31), or 40 mg/m$^2$ given weekly, concurrently with RT. The doses are in line with current medical guidelines (National Comprehensive Cancer Network, American College of Chest Physicians/American Society of Clinical Oncology [ASCO], and European Society for Medical Oncology) with reference to the SoC for concurrent CRT with cisplatin in the treatment of subjects with SCCHN.

## 3.6 Known and Potential Risks and Benefits to Human Subjects

This clinical trial will be conducted in compliance with the ICH E6 GCP Guidance, and any additional applicable regulatory requirements.

The benefit-risk relationship has been carefully considered in the planning of the trial. Based on the CCI [redacted] data on M3814 and on published nonclinical and clinical data showing evidence of cell death and tumor shrinkage after single-agent use in tumors with pre-existing altered repair mechanisms, thus illustrating the concept of synthetic lethality, the conduct of this trial is considered justifiable using the dose(s) and dosage regimen(s) of the IMP as specified in this clinical trial protocol [1, 2, 3].

It is known that RT can cause acute toxicities in the form of, for example, radiation dermatitis and mucositis. Definitive concurrent CRT, considered the SoC for inoperable locoregionally advanced SCCHN, is associated with significant acute toxicities including stomatitis (oral mucositis), swallowing dysfunction (odynophagia, dysphagia), decreased appetite, and dermatitis [4, 5, 6, 7]. For incurable head and neck cancers, RT has been demonstrated to be an effective palliative modality and most acute toxicities are generally related to mucosal inflammation and dermatitis, even though the severity and frequency of these AEs were lower compared with CRT in the curative setting [8]. Late toxicities arising 3 months or later after the end of RT can be seen in the form of, for example, xerostomia, esophagitis, pneumonitis, and fibrosis. Patients should be

reminded to contact the trial site immediately in case of toxicities where they will be evaluated and treated as appropriate according to institutional guidelines. Potentially acute and late toxicities can be more severe when RT is given in combination with M3814. This will be evaluated on an ongoing basis for up to 12 months after the end of treatment.

In this trial, the SMC will monitor the benefit-risk ratio on an ongoing basis. The trial will be discontinued in the event of any new findings that indicate a relevant deterioration of the benefit-risk ratio for the subjects, which would render continuation of the trial unjustifiable.

Based on the available CCI and clinical data to date, the conduct of the trial specified in this protocol is considered justifiable in subjects with locally advanced disease.

# 4 Trial Objectives

## 4.1 Primary Objectives

The primary objectives of the trial are:

- Phase Ia (dose escalation):
  - (Arm A) To determine the maximum tolerated dose (MTD) and a RP2D for M3814 in combination with fractionated palliative RT for tumors or metastases localized in the head and neck region or thorax (3 Gy x 10; 5 F/W).
  - (Arm B) To determine the MTD and a RP2D for M3814 in combination with curatively intended CRT (2 Gy x 33 to 35; 5 F/W with concurrent cisplatin) in treatment-naïve subjects with local/locally advanced SCCHN.
- Phase Ib (disease specific cohort expansion):
  - (Arm A) To evaluate the safety and tolerability of M3814 in combination with fractionated RT (2 Gy x 33; 5 F/W) in treatment-naïve subjects with Stage III A/B NSCLC not eligible for concurrent chemoradiation
  - (Arm B) To evaluate the safety and tolerability of M3814 in combination with CRT (2 Gy x 33 to 35; 5 F/W with concurrent cisplatin) in subjects with treatment-naïve SCCHN.

## 4.2 Secondary Objectives

The secondary objectives of the trial are:

- Phase Ia (dose escalation):
  - To evaluate the safety profile and tolerability of M3814 in combination with palliative RT for tumors or metastases localized in the head and neck region or thorax (Arm A) and in combination with curatively intended CRT in treatment-naïve subjects with SCCHN (Arm B)
  - To explore the antitumor activity of M3814 in combination with RT (Arm A) and CRT (Arm B).

- Phase Ib (disease specific cohort expansion):
  - To explore the efficacy in terms of overall response rate, progression-free survival (PFS) and overall survival (OS) of M3814 in combination with RT (Arm A) or in combination with CRT (Arm B), and local/local regional tumor control (Arm B)
- Phase Ia, Phase Ib, and ancillary cPoP parts: To assess the PK of M3814.

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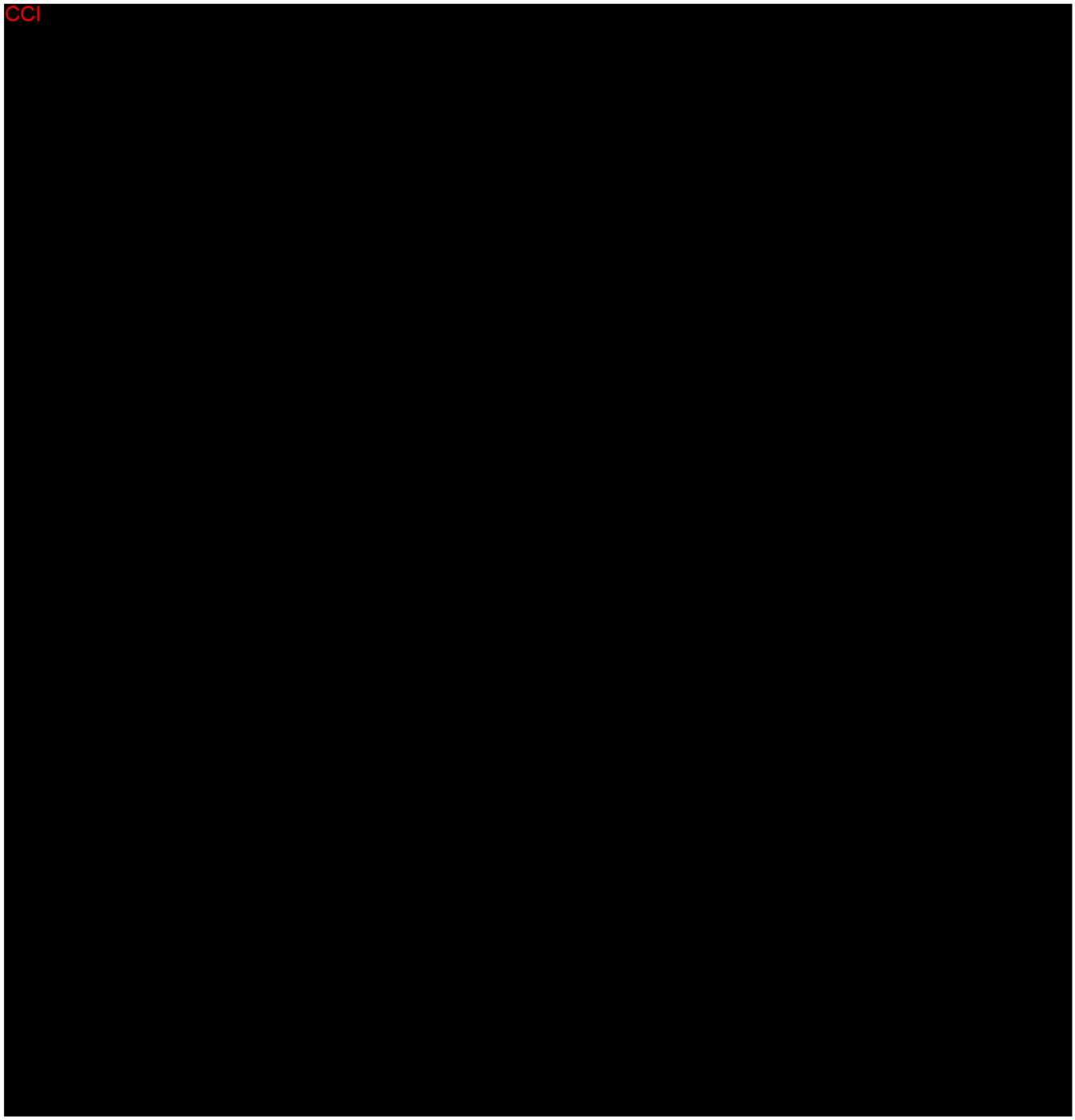


# 5 Investigational Plan

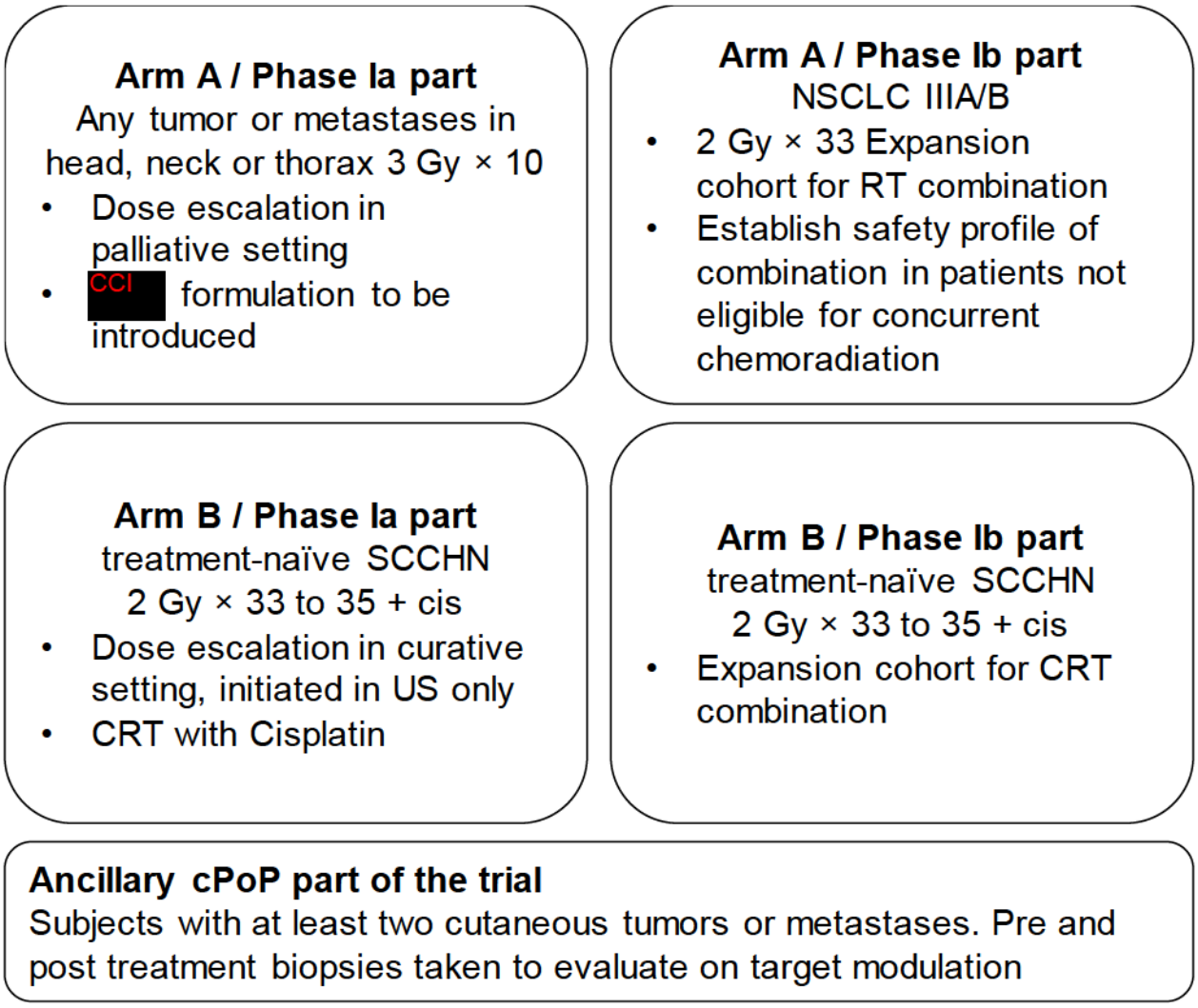
## 5.1 Overall Trial Design and Plan

This is a combined Phase Ia/Ib, open label, dose escalation, and dose expansion trial designed to explore the safety, tolerability, PK and PD profile, and clinical activity of M3814 in combination with RT/CRT, and to determine the MTD and RP2D for M3814 in combination with RT/CRT. An ancillary cPoP part of the trial will be conducted in parallel with the Phase Ia/Ib core trial to explore the PD effect of M3814 in combination with RT on target engagement in tumor tissue.

In the Phase Ia part of the trial, previously treated subjects with locally advanced disease (any tumor or metastases including lymphomas) localized in the head and neck region or thorax that is not amenable to surgical therapy, or with standard systemic therapy with an indication for palliative RT (30 Gy in 10 fractions) will be included in Arm A. After the first dose level (100 mg M3814) in Arm A has been completed, a second dose escalation arm (Arm B) will be initiated at a starting dose of 50 mg M3814 in treatment-naïve subjects with SCCHN, who are eligible for fractionated RT (66 to 70 Gy in 33 to 35 fractions) with concurrent cisplatin. In the Phase Ib part, each arm from Phase Ia will have an expansion cohort. After establishment of RP2D in Arm A, subjects with treatment-naïve Stage III A/B NSCLC not eligible for surgical resection or concurrent chemoradiation will be given M3814 in combination with RT (66 Gy in 33 fractions) in the Arm A expansion cohort. The expansion cohort for Arm B will include treatment-naïve subjects with SCCHN, as specified in Phase Ia and will be given the same CRT (66 to 70 Gy in 33 to 35 fractions with concurrent cisplatin) in combination with M3814 at the RP2D established in Phase Ia Arm B. In the ancillary cPoP part of the trial, subjects with at least 2 (sub)cutaneous tumor/metastases of any type (at least 2 cm apart) with an indication for single high dose palliative RT will be included.

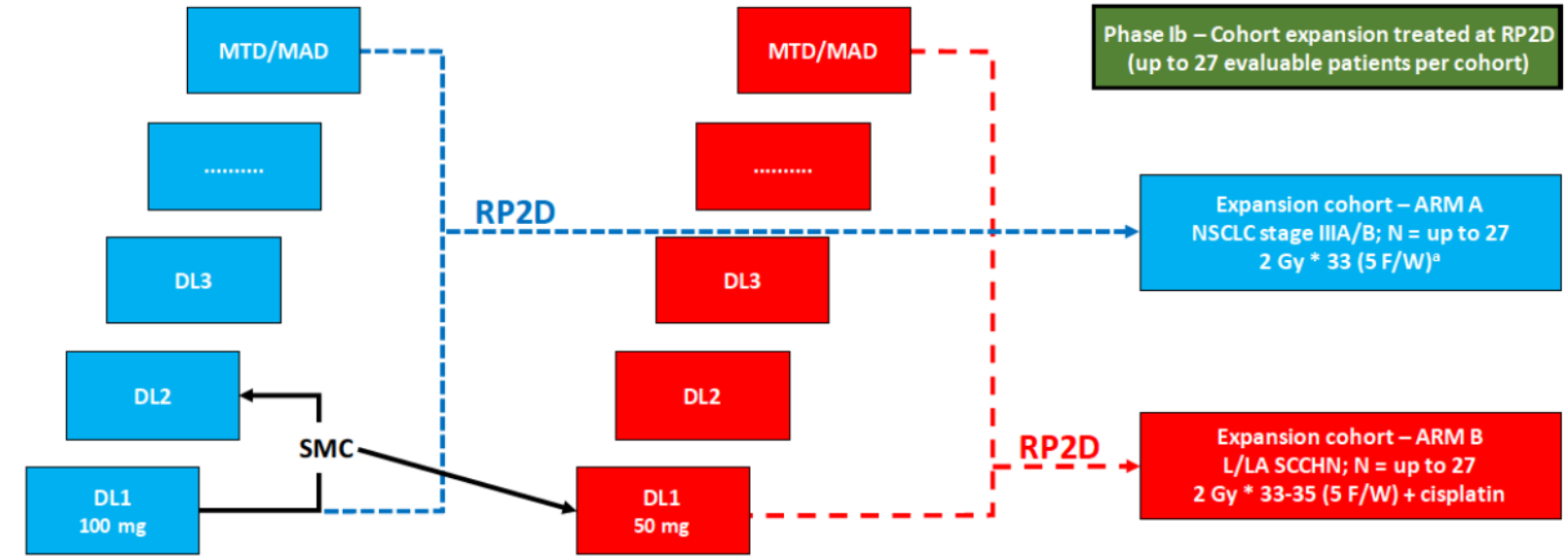
A schematic of the overall trial design is shown in Figure 1, the dose escalation is shown in Figure 2 and the treatment overview with the tablets in Phase Ia Arm A is shown in Figure 3. The Schedule of Assessments is shown for the Phase Ia part of the trial in Table 1 (Arm A - capsule), Table 2 (Arm A – tablet), and Table 5 (Arm B, SCCHN cohort), for the first 3 subjects in the Phase Ib part of the trial (Arm A, NSCLC cohort) in Table 3, for the Phase Ib part of the trial in Table 4 (Arm A, NSCLC cohort) and Table 6 (Arm B, SCCHN cohort), and the ancillary cPoP part of the trial in Table 7. In addition, the schedule of trial treatment and biopsies in the ancillary cPoP part of the trial are outlined in Table 8.

**Figure 1** **Overview of Trial Design with 5 Segments**



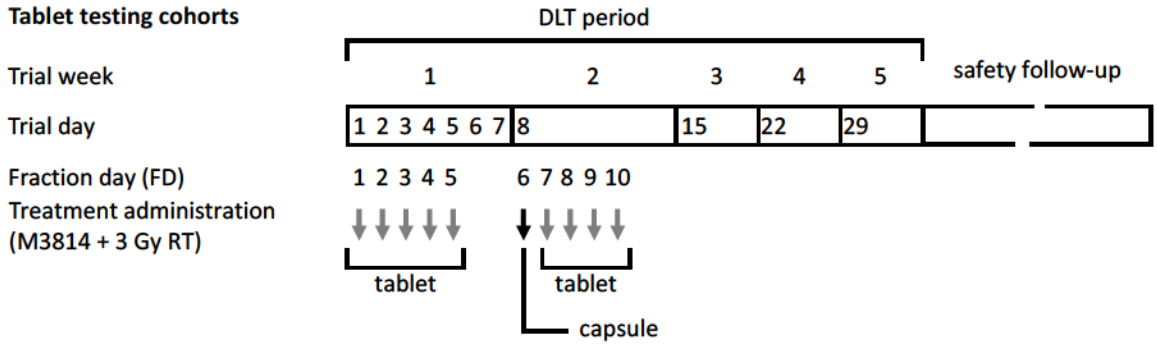

cis = cisplatin; cPoP = clinical proof-of-principle; CRT = chemoradiotherapy; Gy = gray; CCI = CCI
NSCLC = non-small cell lung cancer; RT = radiotherapy; SCCHN = Squamous cell carcinoma head and neck.

**Figure 2 Schematic of Trial Design**




cPoP = clinical Proof-of-Principle; DL = dose level; F/W = fractions per week; H&N = head and neck; CCI = CCI L/LA = local/locally advanced; MAD = maximum administered dose; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; RP2D = recommended phase 2 dose; SCCHN = squamous cell carcinoma head and neck; SMC = Safety Monitoring Committee.

**Figure 3 Treatment Overview (Phase Ia Arm A)**




DLT = dose limiting toxicity; FD = fraction day; Gy = gray; RT = radiotherapy.
Note: the starting dose for the tablet is 50% of the current tolerable capsule formulation.

## Screening Period

After providing informed consent for the trial and the PGx analysis, the eligibility of trial subjects will be established according to the protocol-defined inclusion (Section 5.3.1) and exclusion criteria (Section 5.3.2) during a maximum 21-day Screening Period (screening and baseline evaluations). Once all screening procedures have been completed and it has been confirmed that a subject meets all the eligibility criteria, the subject will be enrolled into the trial and enter the treatment period.

## Treatment Periods

In the Phase Ia part (Arms A and B), subjects will be assigned to a dose determined by the SMC in the next available open treatment cohort guided by a Bayesian logistic regression model with overdose control. Only escalation in the tablet cohort of Arm A will be performed according to a 3+3 design as it is not planned to determine MTD, but rather confirm the RP2D of the capsule formulation. Full details of the dosing regimens for M3814 are provided in Section 6.3. All treatment with M3814 will be given in combination with RT only in Arm A, and in combination with CRT in Arm B.

Throughout the treatment period, subjects in all cohorts will attend regular trial visits for dosing, safety evaluations and blood sampling for PK and PD, as described in Section 7.

Phase Ia

Following completion of the screening and baseline evaluations, subjects included in the Phase Ia, Arm A, part of the trial will receive treatment with M3814 at a starting dose of 100 mg QD for 2 consecutive weeks during the period RT (3 Gy x 10, 5 F/W) is given. The administration of M3814 will take place 1.5 hours (± 30 minutes) before the start of RT.

In Arm A, the subjects in the dose escalation part will receive the capsule formulation of M3814 throughout, except for the subjects in the tablet testing cohorts, who will receive the capsule

formulation at the same dose as the tablet formulation on FD6, and the tablet formulation on all other fraction days.

Following completion of the screening and baseline evaluations, subjects included in the Phase Ia, Arm B part of the trial will receive treatment with M3814 at a starting dose of 50 mg QD for 7 consecutive weeks. During this period, RT (2 Gy x 33 to 35, 5 F/W) is given with concurrent cisplatin administration. The administration of M3814 will take place 1.5 hours (± 30 minutes) before the start of RT. This arm will be initiated after the first dose level (100 mg) in Arm A has been completed and evaluated by the SMC.

The dose escalation in Arm B will commence with the capsule formulation. Based on the findings in the tablet testing cohorts from Arm A, the SMC may decide to introduce the tablet formulation in Arm B. Subjects will only receive one formulation during their treatment.

In both arms, dose escalation will continue from the starting dose of M3814 up to a maximum dose of M3814 800 mg/day until one of the following stopping rules apply: a maximum number of 30 subjects are included, more than three cohorts are assigned to the same dose level or the estimate for DLT probability of the MTD reaches sufficient precision. It is anticipated that up to 30 evaluable subjects (10 cohorts of 3 subjects) may be needed in each arm in order to determine the MTD of M3814 (see Section 8 for details).

Phase Ib

Following completion of the screening and baseline evaluations (see Section 5.3 for entry criteria), subjects enrolled in the Phase Ib part of the trial (expansion cohort for Arm A - NSCLC) will receive M3814 QD at one dose level below the RP2D, to be given 1.5 hours (± 30 minutes) before each RT (2 Gy) fraction for up to 33 fractions. The first 3 NSCLC subjects included in the Phase Ib (Arm A) part will be treated with M3814 one dose level below the RP2D to evaluate the safety of M3814 when given to subjects in the curative setting. Based on the safety profile seen in the first 3 subjects, the SMC will decide if the dose of M3814 can be escalated to the RP2D. It is planned to enroll up to 27 evaluable subjects with Stage III A/B NSCLC in the Phase Ib (Arm A) part of the trial, and a further expansion cohort for Arm B (SCCHN) is planned to enroll up to 27 evaluable subjects with SCCHN, using the RP2D defined in Phase Ia, Arm B.

Ancillary cPoP part

Following completion of the screening and baseline evaluations, subjects enrolled in the ancillary cPoP part of the trial will receive a single high dose of RT (10-25 Gy) on Lesion 1 on Day 1 and on Lesion 2 on Day 2. A single dose of the capsule formulation of M3814 will be administered on Day 2, 1.5 hours (± 30 minutes) before the start of RT (see Section 6.3.2 for details on dosing). Three fixed dose levels are planned (100 mg, 200 mg, and 400 mg) (see Table 12 for details).

The ancillary cPoP part of the trial will initially be conducted with the capsule; however, additional cohorts of M3814 (CCI formulation) may be introduced. The starting dose and subsequent dose levels of M3814 (CCI formulation) will be defined by the SMC based on PK and safety data generated in ongoing clinical studies evaluating the safety, tolerability, PK, and PD of M3814 (CCI formulation).

It is planned to enroll 11 subjects with (sub)cutaneous tumor/metastases in the ancillary cPoP part of the trial using M3814 capsule formulation and approximately 12 additional subjects with (sub)cutaneous tumor/metastases using M3814 CCI formulation.

**Follow-up Periods**

Phase Ia/Ib

The follow-up period for all subjects in the Phase Ia and Ib parts of the trial will consist of the following:

- DLT Period: A 5-week (Arm A) or 12-week (Arm B) DLT period after the first dose of M3814 for the evaluation of 'acute' systemic and local toxicity in all subjects in Phase Ia and a 12-week DLT period after the first dose of M3814 in the first 3 subjects of the safety run-in part in the NSCLC expansion cohort during Phase Ib (Arm A)
- Short-term Safety Follow-up: A follow-up for a period of 30 days after the end of RT for evaluation of safety
- Mid-term Safety Follow-up: A safety follow-up period of 3 months after end of RT to evaluate signs of RT-induced toxicity on normal surrounding tissues
- Long-term Safety Follow-up: A safety follow-up period until 12 months after end of RT to evaluate late signs of RT-induced toxicity on normal surrounding tissues
- Survival Follow-up: A follow-up period that will continue until 12 months after the last subject has stopped RT/CRT.

Ancillary cPoP part

Subject overall safety will be evaluated up to Day 10 (Follow-up Period). Local tolerability will be reported on Days 10 and 32 (Days 8 and 30 after the end of treatment, Safety Follow-up Period). In addition, on Day 10 local tumor response will be assessed in irradiated lesions (only applicable for additional cohorts of M3814 [CCI formulation]). Subjects will be permitted to receive any indicated systemic therapeutic modality as soon as clinically indicated after Day 10.

### 5.1.1 Dose Escalation Rules

The criteria for dose escalation are based on the occurrence of AEs and/or DLTs that are unrelated to underlying conditions and/or to concomitant medication during the DLT period in evaluable subjects in each cohort. The DLT window of 5 weeks (Phase Ia, Arm A) or 12 weeks (Phase Ia, Arm B and the first 3 subjects in the expansion cohort for Arm A [NSCLC]) after the start of M3814 treatment allows an evaluation of acute toxicity. M3814 dose escalation will not proceed to the next dose level until all subjects in the previous dose level have been observed for the duration of the DLT period. However, RT/CRT and the combination of RT/CRT and M3814 can also give rise to later toxicities. A 3-month mid-term safety follow-up will be performed in all subjects in the Phase Ia part of the trial and, once available, these data will also guide subsequent dose escalation and the establishment of the RP2D. Available PK and PD data will also be taken into consideration.

**Dose Escalation During Phase Ia**

A Bayesian two-parameter logistic regression model with overdose control will be used to assist the SMC with dose selection during the Phase Ia dose escalation (capsule formulation in Arm A/B, and tablet formulation in Arm B). Cohorts of 3 subjects each will be treated at the same dose level (capsule starting dose: 100 mg QD for Arm A and 50 mg QD for Arm B). The model incorporates prior information (from nonclinical data) and observed information from each completed cohort (and data from all previous cohorts) to provide a recommended dose for the next cohort. A preselected set of acceptable doses are considered by the model, however doses which are not part of the prespecified set may be chosen as well. The model ensures that recommended doses correspond to a probability of less than 25% that the true DLT rate is more than 35% in Arm A and 45% in Arm B. Dose escalation will stop in each arm as soon as the first of the following stopping rules apply: a maximum of 30 subjects are included, more than three cohorts are assigned to the same dose level, or the estimate of DLT probability at the MTD reaches a sufficient precision (see Section 8 for more details).

Selection of the RP2D determined with the capsule formulation will be performed in Phase Ia Arm A based on the available clinical information already generated with the M3814 capsule at escalating doses. Therefore, it is anticipated that a smaller number of dose cohorts and subjects will be required to reassess safety, tolerability and PK of M3814 after dosing with the tablet formulation in combination with RT by use of standard 3+3 dose escalation design criteria (see Section 5.1.2 for more details).

**Dose Escalation During Phase Ib**

Following completion of the screening and baseline evaluations, treatment-naïve subjects with Stage III A/B NSCLC enrolled in the Phase Ib part of the trial (Arm A expansion cohort) will receive M3814, to be given 1.5 hours (± 30 minutes) before each RT fraction for 33 fractions. The dose of M3814 for the first 3 subjects will be established from the available data in both arms of the Phase Ia part of the trial. In case a RP2D in Arm B has been established before a RP2D from Arm A, then the Arm A expansion cohort can be initiated at the RP2D identified in Arm B. In case a RP2D has been established first in Arm A, the first 3 subjects will be treated one dose level below the RP2D. Based on the safety profile, the SMC will decide if the dose can be escalated to the RP2D identified in Phase Ia, Arm A.

The dose in the Arm B expansion cohort will be the determined RP2D of M3814 from Phase Ia Arm B and will be given to subjects with treatment-naïve SCCHN in combination with the same CRT regimen as in Phase Ia (Arm B).

**Doses of M3814 in the Ancillary cPoP Part of the Trial**

In the ancillary cPoP part of the trial, the doses are fixed at 100 mg, 200 mg, and 400 mg. After the three planned cohorts, additional cohort(s) might be opened upon SMC decision.

The single dose of M3814 to be administered on Day 2 of the ancillary cPoP part of the trial is fixed for successive cohorts as shown in Table 12.

The ancillary cPoP part of the trial will initially be conducted with the capsule; however, additional cohorts of M3814 (CCI formulation) may be introduced. The starting dose and subsequent dose levels of M3814 (CCI formulation) will be defined by the SMC based on PK and safety data generated in ongoing clinical studies evaluating the safety, tolerability, PK, and PD of M3814 (CCI formulation).

**Table 12 Doses of M3814 in the Ancillary cPoP Part of the Trial**

| Dose (mg)[a] | Number of subjects included[b] |
|---|---|
| 100 | 3 |
| 200 | 3 |
| 400 | 3 |
| (> 100 / < 400)[c] | (3) |

cPoP = clinical proof-of-principle; CCI = CCI PK = pharmacokinetics; RP2D = recommended Phase II dose; SMC = Safety Monitoring Committee.

a. Additional cohorts of M3814 (CCI formulation) may be introduced. The starting dose and subsequent dose levels of M3814 (CCI formulation) will be defined by the SMC based on PK and safety data generated in ongoing clinical studies evaluating the safety, tolerability, PK, and pharmacodynamics of M3814 (CCI formulation).
b. At the RP2D an additional 2 subjects will be included making 5 subjects at the RP2D.
c. Additional doses might be opened upon SMC decision.

### Dose Interruption and Dose Reduction

Please refer to Section 6.3.1 for detailed information.

All treatment with M3814 will be given in combination with RT; therefore, a delay in RT would lead to a delay in treatment with IMP. See Section 6.6.3.1 for details on handling RT treatment delays.

### Definition of Dose Limiting Toxicity

Dose limiting toxicities will be used to determine dose escalation, same dose level extension, and de-escalation and to determine the MTD taking into account the known toxicities with RT alone. DLT is defined in Section 7.4.1.5.

### Definition of MTD

The MTD will be defined by the SMC based on the results from all dose escalation cohorts within each arm. See Section 8.1 for details.

### Endpoints

Safety will be the primary endpoint for dose escalation in this trial. Other endpoints (PK, PD, efficacy) if available will also be considered. Endpoints are presented in Section 8.3.

### Termination of Treatment

Treatment with M3814 will continue until scheduled RT is completed, unacceptable toxicity, withdrawal of consent, or any criterion for withdrawal from IMP occurs (see Section 5.5.1 for criteria). In all cases, when a subject has discontinued all trial treatments for any reason, the Early

Treatment Termination (ETT) visit should be performed. An End of Trial (EOT) visit will be performed on Post-treatment Day (PTD) 365 for those subjects that remain in the trial or in case of premature trial discontinuation prior to PTD Day 365 (see Section 7.1.4).

**Withdrawal from the Trial**

Subjects will be withdrawn from the trial if they withdraw consent for any further follow-up visits. See Section 5.5.2 for more details.

### 5.1.2 Tablet Formulation Introduction, Evaluation, and SMC Decision Making

In addition to the capsule formulation used in this and previous studies, a tablet formulation has been developed. Owing to its formulation characteristics, dissolution of the drug substance may be enhanced in the tablet compared to the capsule formulation. CCI [redacted] Physiology-based (GastroPlus) modeling of the human absorption which is predicted to be > 90% at daily doses up to 400 mg, and > 50% at daily doses up to 1000 mg. To take a conservative approach, exposure increases of 2-fold relative to the capsule formulation is assumed.

Currently doses and exposures of up to 200 mg QD of the capsule formulation in combination with RT are considered safe and well tolerated by the SMC. Dose escalation in the current trial is ongoing and the dose of 300 mg is currently being tested. Considering the scenario of an exposure increase of 2-fold of the tablet relative to the capsule formulation a starting dose of 100 mg QD has been selected.

**Introduction of the tablet in the Phase Ia part of Arm A**

The tablet formulation will be introduced in Phase Ia Arm A of this trial taking into account the available clinical experience and exposure reached after administration of the capsule formulation of M3814 in combination with RT. Subjects will receive the tablet formulation at a starting dose of 100 mg QD on trial days FD 1-5 and FD 7-10. On trial day FD 6, the current capsule formulation will be given as a single dose of 100 mg to allow an intra-individual cross over comparison of single dose PK between the tablet and the capsule formulation. The administration of M3814 formulations will take place 1.5 hours (± 30 minutes) before the start of RT. In subsequent dose levels tablet and capsule formulations will always be given using the same dose.

After an initial cohort of 3 patients has been treated at the initial tablet dose of 100 mg, the SMC will decide to treat further patients at this tablet dose with the same dose, or to test optional dose levels (either decreases or increases of dose, the nominal dose will be the same as for the tablets). To decide on the doses to be tested, the SMC will review all available safety, tolerability and PK data, e.g., $t_{max}$, $C_{max}$, $AUC_{0-24}$ after single doses of the capsule (FD6) and the tablet (FD1) formulations. The goal is to achieve exposures close to those achieved at the RP2D established for the capsule.

It is foreseen to test up to 6 subjects per tablet dose level.

**Introduction of the tablet in other parts of the trial**

The Phase Ib part of Arm A may be performed using the M3814 tablet formulation. The first 3 patients of this part will be treated with a dose one dose level below the RP2D determined in the Phase Ia part of Arm A. The SMC will review all available safety, tolerability, and PK data from this cohort and decide on the M3814 dose to be administered to the remaining subjects of this arm.

Based on all available safety, tolerability, and PK data after administration of the tablet in Arm A of the trial, the SMC may decide to change the formulation in the Phase Ia part of Arm B from the capsule to the tablet. This will be done during a dose escalation decision. The selection of the respective tablet dose will take into account the differences in exposure between the capsule and tablet.

The Phase Ib part of Arm B may be conducted using the tablet formulation at the RP2D for the combination with RT and cisplatin identified in the respective Phase Ia part of Arm B.

The ancillary cPoP part of the trial will initially be conducted with the capsule formulation; however, additional cohorts of M3814 (CCI formulation) may be introduced. The starting dose and subsequent dose levels of M3814 (CCI formulation) will be defined by the SMC based on PK and safety data generated in ongoing clinical studies evaluating the safety, tolerability, PK, and PD of M3814 (CCI formulation).

## 5.2 Discussion of Trial Design

This Phase Ia/Ib, open label trial comprises a dose escalation part (Phase Ia) in which the safety and tolerability of M3814 in combination with RT (and with concurrent cisplatin in Arm B) will be explored in subjects with advanced solid tumors, metastases or lymphomas localized in the head and neck region or thorax (Arm A) and in treatment-naïve subjects with SCCHN (Arm B) to determine MTD and RP2D. The subsequent dose expansion Phase Ib part of the trial will evaluate the safety and explore the efficacy of M3814 in combination with RT in subjects with NSCLC and in combination with CRT (RT and cisplatin) in subjects with SCCHN. In addition, an ancillary cPoP part of the trial will run in parallel with the Phase Ia/Ib parts of the trial to explore the PD of M3814 in combination with RT on target engagement in tumor tissue.

The inclusion and exclusion criteria were chosen to maximize the potential for subject safety and possible benefit from M3814 in combination with RT.

An open label design is considered appropriate for a dose escalation trial with a subsequent expansion cohort in subjects with cancer.

The first cohort of 3 subjects in the Phase Ia, Arm A part of the trial will receive M3814 at a dose of 100 mg and in the Phase Ia, Arm B part of the trial will receive 50 mg, as described in Section 3.3 and Section 3.3.1. Thereafter the trial design for dose escalation employs a Bayesian escalation approach and sequential cohorts of 3 subjects in order to determine the MTD and to enable the SMC to select the next dose from a predicted set of acceptable doses. This design aims to maximize the protection of trial subjects by reducing the number exposed to possible drug

toxicities at each new dose. The SMC may decide to stop dose escalation at any dose level based on safety and PK data.

Introduction and evaluation of the tablet will be performed in the Phase Ia, Arm A part of the trial. A first cohort of patients will receive the tablet formulation at a dose of 100 mg. Based on the previous clinical experience with the M3814 capsule doses up to 400 mg in the ongoing dose escalation, and the anticipated maximal exposure after administration of the tablet, the initial tablet dose of 100 mg in the first tablet cohort is expected to be safe and well-tolerated.

After review of the safety, tolerability, and PK data from this cohort in relation to the data obtained in the ongoing dose escalation, the SMC may decide to test further tablet dose levels. The aim is to confirm the RP2D that has been defined for the capsule, using the tablet formulation.

The design of the tablet testing cohorts in the Phase Ia part of Arm A also includes intra-individual comparison of single dose PK of M3814 after administration of the tablet versus capsule. The capsule administered on FD6 after a 48-hour wash-out is not expected to be influenced by the previous administration of M3814 tablets on FD1 to FD5, considering the median terminal half-life of 5.5 hours (range 2.0 to 8.8 hours, preliminary data estimated in the CCI [redacted]) after multiple daily dosing. Clinical safety, tolerability, and PK results obtained in Phase Ia Arm A will determine subsequent introduction of the tablet in other parts of the trial.

### 5.2.1 Inclusion of Special Populations

Not applicable.

## 5.3 Selection of Trial Population

Only subjects meeting all inclusion criteria and none of the exclusion criteria may be enrolled into the trial. Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject has provided written informed consent following the procedure described in Section 9.2.

For subjects in Phase Ia and Ib, archival tumor material must be available, either as a block or slides (most recent material). If no archival material is available then a fresh biopsy should be taken. All subjects in the ancillary cPoP part of the trial must agree to have tumor biopsies collected.

### 5.3.1 Inclusion Criteria

To be eligible the subject must fulfill all of the following criteria:

1. Subjects must have:

    a. **Phase Ia part**: advanced solid tumors or metastases including lymphoma localized in the head and neck region or thorax with an indication for fractionated palliative RT (Arm A); or treatment-naïve SCCHN eligible for fractionated curatively intended RT with concurrent cisplatin (Arm B)

b. **Phase Ib part**: treatment-naïve Stage III A/B NSCLC not eligible for surgical resection or concurrent chemoradiation (Arm A expansion cohort) or treatment-naïve SCCHN eligible for fractionated curatively intended RT with concurrent cisplatin (Arm B expansion cohort)

c. **Ancillary cPoP part**: any tumor with at least 2 (sub)cutaneous tumor/metastases at least 2 cm apart which are RT naïve with an indication for high dose palliative RT

2. Measurable or evaluable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (not required for the ancillary cPoP part of the trial)

3. Male or female subjects at least 18 years of age

4. Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1

5. Must have read, well understood, and signed and dated the Informed Consent Form (ICF); the subject fully understands the requirements of the trial and is willing to comply with all trial visits and assessments

6. A male participant must agree to use and to have their female partners to use a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in Appendix E of this protocol 14 days before first dose of trial treatment, during the treatment period and for at least 90 days after the last dose of trial treatment and refrain from donating sperm during this period

7. A female participant is eligible to participate if she is not pregnant (see Appendix E), not breastfeeding, and at least one of the following conditions applies:

   a. Not a woman of childbearing potential (WOCBP) as defined in Appendix E

   OR

   b. A WOCBP who agrees to use a highly effective contraception (ie, methods with a failure rate of less than 1% per year), as detailed in Appendix E of this protocol, 14 days before the start of first dose of trial treatment, during the treatment period and for at least 90 days after the last dose of trial treatment

8. Life expectancy of ≥ 3 months (Phase Ia, Arm A) or ≥ 6 months (Phase Ia, Arm B and Phase Ib).

### 5.3.2 Exclusion Criteria

#### 5.3.2.1 Phase Ia/Ib Parts

Subjects are not eligible for the Phase Ia or Ib parts of the trial if they fulfill any of the following exclusion criteria:

1. Prior treatment consisting of:

    a. Chemotherapy, immunotherapy, hormonal therapy, biologic therapy, or any other anticancer therapy or IMP within 28 days of first trial drug intake (6 weeks for nitrosoureas or mitomycin C) for Phase Ia, Arm A subjects, and any prior therapy for Phase Ib subjects. For subjects with rapidly growing tumors localized in the head and neck region or thorax where the treating physician cannot wait for 28 days, inclusion may take place if there is no residual toxicity from previous treatment (maximum Common Terminology Criteria for Adverse Events [CTCAE] Grade 1)

    b. Prior RT to the same region within 12 months (Phase Ia, Arm A; subjects with tumors localized in the head and neck region or thorax) or at any time previously (Phase Ia, Arm B; treatment-naïve subjects with SCCHN and Phase Ib; treatment-naïve subjects with Stage III A/B NSCLC or SCCHN)

    c. Extensive prior RT on ≥30% of bone marrow reserve as judged by the Investigator or prior bone marrow/stem cell transplantation within 5 years before trial start

2. Residual toxicity due to prior therapy with no return to baseline or ≤ Grade 1 (except alopecia according to CTCAE v4.03)

3. Surgical intervention, including biopsies and dental root surgeries, within 28 days prior to the first dose of IMP administration or having participated in an interventional clinical trial within 28 days prior to the first dose of IMP administration for Phase Ia/Ib. **Needle biopsies are not considered as surgery.**

4. Poor vital organ functions defined as:

    a. Bone marrow impairment as evidenced by hemoglobin <10.0 g/dL (5.7 µmol/L), neutrophil count $<1.0 \times 10^9$/L, platelets $<100 \times 10^9$/L

    b. Renal impairment as evidenced by serum creatinine >1.5 × upper limit of normal (ULN)

    c. Liver function abnormality as defined by total bilirubin >1.5 × ULN or aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >2.5 × ULN (except for subjects with liver involvement, who can have AST/ALT >5 × ULN)

5. Significant cardiac conduction abnormalities, including a history of long QTc syndrome and/or pacemaker, or impaired cardiovascular function such as New York Heart Association classification score > 2

6. Hypertension uncontrolled by medication

7. Known CNS metastases unless previously treated by RT, stable by computed tomography (CT) scan for at least 3 months without evidence of cerebral edema and no requirement for corticosteroids or anticonvulsants

8. Known human immunodeficiency virus (HIV) positivity, known clinically significant history of hepatitis (e.g., Hepatitis B [HBV] or Hepatitis C [HCV] virus), current alcohol abuse, or cirrhosis. Screening for HIV to be performed according to local practice and local regulatory guidance. Testing for HIV and HBV/HCV should be repeated if the subject tested negative for the viruses more than 3 months before trial enrollment

9. Ongoing active infection other than HIV, HBV or HCV, or treatment with a live attenuated vaccine within 30 days of dosing

10. History of difficulty swallowing, malabsorption or other chronic gastrointestinal disease or conditions that may hamper compliance and/or absorption of the IMP, current use of percutaneous endoscopic gastrostomy (PEG) tubes

11. History of any other significant medical disease such as major gastric or small bowel surgery, recent drainage of significant volumes (as per Investigator's judgement) of ascites or pleural effusion or a psychiatric condition that might impair the subject's well-being or preclude full participation in the trial

12. Known hypersensitivity to the trial treatment or to one or more of the excipients used

13. Pregnancy or lactation period

14. Legal incapacity or limited legal capacity

15. Subjects currently receiving (or unable to stop using prior to receiving the first dose of trial drug) medications or herbal supplements known to be potent inhibitors of CYP3A or CYP2C19 must stop at least 1 week prior to taking M3814. Subjects receiving potent inducers of CYP3A or CYP2C19 must stop at least 3 weeks prior to taking M3814. Those receiving drugs mainly metabolized by CYP3A with a narrow therapeutic index as judged by the Investigator (and after optional consultation with the Sponsor) must stop at least one day prior to taking M3814.

16. Subjects currently receiving $H_2$-blocker or proton pump inhibitors (PPIs) (or unable to stop at least 5 days prior to the first treatment).

17. If the planned radiation field includes any part of the esophagus and the subject has symptoms of ongoing esophagitis, the subject is not eligible, unless an esophageal endoscopy rules out the presence of esophagitis.

18. Subjects where more than 10% of the total esophagus volume receives more than 50% of the prescribed RT dose.

Out of range laboratory values may be retested within the timeframe of the screening period.

#### 5.3.2.2 Ancillary Clinical Proof-of-Principle Part

Subjects are not eligible for the ancillary cPoP part of the trial if they fulfill any of the following exclusion criteria:

1. History of difficulty swallowing, malabsorption or other chronic gastrointestinal disease or conditions that may hamper compliance and/or absorption of the IMP
2. History of any other significant medical disease such as major gastric or small bowel surgery, recent drainage of significant volumes of ascites or pleural effusion (as per Investigator's judgement) or a psychiatric condition that might impair the subject's well-being or preclude full participation in the trial
3. Known hypersensitivity to the trial treatment or to one or more of the excipients used
4. Pregnancy or lactation period
5. Legal incapacity or limited legal capacity
6. Subjects currently receiving (or unable to stop using prior to receiving the first dose of trial drug) medications or herbal supplements known to be potent inhibitors of CYP3A or CYP2C19 must stop at least 1 week prior to taking M3814. Subjects receiving potent inducers of CYP3A or CYP2C19 must stop at least 3 weeks prior to taking M3814. Those receiving drugs mainly metabolized by CYP3A with a narrow therapeutic index as judged by the Investigator (and after optional consultation with the Sponsor) must stop at least one day prior to taking M3814.

## 5.4 Criteria for Initiation of Trial Treatment

This is an open label trial without randomization. Subjects who provide written informed consent and who meet all relevant eligible criteria will receive open label M3814 at the currently recruiting cohort dose level.

## 5.5 Criteria for Subject Withdrawal

### 5.5.1 Withdrawal from Trial Therapy

The subject must be withdrawn from IMP in the event of any of the following:

- Occurrence of an exclusion criterion which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor prior to treatment completion
- Therapeutic failure requiring urgent additional drug (if applicable)
- Discontinuation of RT
- Adverse drug reactions (ADRs) that cause RT delays of >7 days

- Occurrence of AEs, if discontinuation of trial drug is desired or considered necessary by the Investigator and/or the subject (if applicable)
- Occurrence of pregnancy
- Use of a nonpermitted concomitant drug, as defined in Section 6.6, where the predefined consequence is withdrawal from the IMP
- New standard existing therapy that is considered more suitable according to the Principal Investigator
- Noncompliance that is deemed by the Investigator or the Sponsor to compromise subject safety or trial integrity.

### 5.5.2 Withdrawal from the Trial

Subjects are free to discontinue the trial at any time without giving their reasons.

A subject must be withdrawn in the event of any of the following:

- Withdrawal of the subject's consent
- Participation in any other trial during the duration of this trial (up to 12 months in Phase Ia and Ib parts and up to 32 days in the ancillary cPoP part)
- Pregnancy prior to treatment completion or up to 30 days after RT.

If a subject has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of premature withdrawal from the trial, assessments for Fraction Day 10 (Arm A) or last Fraction Day (33 to 35; Arm B) in Phase Ia, Fraction Day 33 (NSCLC cohort) or last Fraction Day (33 to 35; SCCHN cohort) in Phase Ib and the EOT visit should be performed, if possible with focus on the most relevant assessments (Table 1 [Phase Ia – Arm A capsule cohorts], Table 2 [Phase Ia – Arm A tablet cohorts], Table 3 [first 3 subjects in Phase Ib – Arm A, NSCLC cohort], Table 4 [Phase Ib – Arm A, NSCLC cohort], Table 5 [Phase Ia: – Arm B, SCCHN cohort], Table 6 [Phase Ib – Arm B, SCCHN cohort], and Table 7 [ancillary cPoP part of the trial]). In any case, the appropriate electronic Case Report Form (eCRF) section must be completed.

## 5.6 Premature Termination of the Trial

The clinical trial may be terminated prematurely at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable benefit-risk judgment (e.g., due to evidence of inadequate drug exposure; occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions; or other unfavorable safety findings in this trial or the FIM trial or any other trial).

The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment making completion of the trial within an acceptable time frame unlikely, or because of discontinuation of clinical development of M3814.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

## 5.7 Definition of End of Trial

The trial will end after the last subject in the Phase Ib part has completed the 1-year follow-up period or all subjects in the ancillary cPoP part of the trial have completed the 30-day follow up, whichever comes later.

# 6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical trial, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

In this trial, the term "Investigational Medicinal Product" refers to the investigational drug M3814, which is the only IMP used in this trial.

## 6.1 Description of the Investigational Medicinal Product

MSC2490484A, International Union of Pure and Applied Chemistry name (S)-[2-chloro-4-fluoro-5-(7-morpholin-4-yl-quinazolin-4-yl)-phenyl]-(6-methoxy-pyridazin-3-yl)-methanol, is supplied as 10 mg (size 4, ivory), 50 mg (size 0, ivory), and 100 mg (size 0, Swedish orange) hard gelatin capsules, as well as 50 mg (beige to yellow caplet) film-coated tablets for oral administration. Capsules consist of bulk drug substance filled into hard gelatin capsules of different size and/or color, depending on the dose strength. No further excipients are used. Hard gelatin capsule shells meet the supplier's (Capsugel®) standards and gelatin is of pharmacopoeial grade.

Film-coated tablets consist of a tablet core composed of extrudate (20% (w/w) drug substance/80% (w/w) copovidone solid dispersion) and other excipients CCI [redacted]. All excipients used in the tablet formulation are of compendial grade. Supplier's certificates show that there is no transmissible spongiform encephalopathy risk.

MSC2490484 capsules and tablets are provided in CCI [redacted] and should be stored CCI [redacted]. The tablets should not be frozen.

## 6.2 Description of Concurrent Chemotherapy

Chemotherapy will be administered in combination with the IMP (M3814) in subjects enrolled in Arm B. The chemotherapy agent is cisplatin which is considered SoC for this indication. This chemotherapeutic agent is administered via intravenous (iv) infusion. Dose and dose regimen of cisplatin is to be applied in line with current medical guidelines (National Comprehensive Cancer Network, American College of Chest Physicians/ASCO, and European Society for Medical Oncology) with reference to the SoC for concurrent CRT with cisplatin in the treatment of subjects

with SCCHN. Two cisplatin dosing schedules are allowed, 100 mg/m$^2$ given twice or 40 mg/m$^2$ given weekly during the RT treatment. In addition to medical guidelines, dosing of cisplatin is to be performed in accordance with the product labeling and clinical site's specific policies/instructions. Cisplatin will not be supplied by the Sponsor. It will be used from commercially available sources and prepared in accordance with its product labeling.

## 6.3 Dosage and Administration

### 6.3.1 Phase Ia and Ib Parts

Subjects with locally advanced disease, as described in the Eligibility Criteria (Section 5.3), will be assigned to receive M3814 at a starting dose of 100 mg QD (Arm A) or 50 mg QD (Arm B) which will be given 1.5 hours (± 30 minutes) before each RT fraction for up to 10 fractions (Arm A) or for 33 to 35 fractions (Arm B).

In the Phase Ia part of the trial and for the first 3 subjects in Phase Ib (NSCLC expansion cohort), the dose of M3814 will be increased according to the dose escalation rules described in Section 5.1.1. No intrasubject dose escalation is permitted.

Subjects will take their assigned dose of M3814 QD with a full glass of water (approximately 240 mL/8 fluid ounces).

Subjects will be instructed as follows:

- On days with serial PK collections (Fraction Days 1 and 10), to fast 1.5 hours prior to dose administration and continue to fast for 4 hours postdose
- On all other Fraction Days, to fast 1.5 hours prior to dose administration and continue to fast for 1 hour postdose
- Take the prescribed dose of M3814 1.5 hours (± 30 minutes) before RT is started
- Swallow the capsules or tablets whole and not bite into the capsules, break or open them, or attempt to dissolve the contents in water prior to taking their assigned dose
- The doses on Fraction Days 1, 2, 6 and 10 should not be taken until the predose PK collection has been completed.

If a subject vomits after taking their dose of M3814, they should be given an antiemetic but no further dose will be given that day. Prophylactic antiemetics should then be given prior to subsequent doses of M3814. Any change from dosing schedule, dose interruptions, or dose reductions should be recorded in the eCRF.

The formal criteria for M3814, RT, and cisplatin dose modification in the trial are included in Table 13.

In general, each subject will stay on the M3814, RT and cisplatin (as applicable) dose level assigned in the trial unless treatment needs to be interrupted, modified or stopped. In all other situations, if the Investigator believes that a treatment-emergent adverse event (TEAE) is due to

cisplatin, the dose is to be modified according to the package insert/SmPC or local guidelines. A cisplatin dose delay of up to 1 week is permitted, in addition to the specific guidance provided below.

M3814 will be provided as tablet formulation of 50 mg for oral administration. Dosing schedule of the tablet formulation follows the description given for the capsule formulation above. The tablet formulation will be initially assessed in Phase Ia Arm A taking into account the available safety, tolerability and PK results from the capsule. Standard 3+3 dose escalation design criteria will apply. Comparison of single dose PK data between the tablet and the capsule will guide to define the tablet doses in Phase Ia Arm B and in the Phase Ib parts.

For subjects in Arm B receiving cisplatin:

- There will be no dose escalation of cisplatin above the protocol-specified dose. However, cisplatin dose re-escalation after an initial dose reduction, following the manufacturer's label, is permitted.
- Dose modifications for toxicity should be independently assessed prior to dose administration at each visit following institutional guidelines or Table 13 in the absence of such guidelines.
- Prophylactic granulocyte-colony stimulating factor (G-CSF) may be implemented if neutropenia results in dose reduction or dose delay at prior doses, as suggested in the ASCO guidelines. Therapeutic use of hematopoietic colony-stimulating factors is permitted following ASCO guidelines.
- In the event a subject experiences neutropenia, and G-CSF is initiated, and neutropenia recovers within 48 hours after beginning treatment with G-CSF, G-CSF may be implemented in the management of neutropenia in this subject to avoid dose reductions or holding a dose.

Hemoglobin must be ≥10 g/dL at FD 1 and must be ≥9 g/dL for all subsequent doses. If hemoglobin is <9 g/dL then appropriate measures according to standard clinical practice must be taken prior to any further dose administration.

## Table 13 Dose Modifications for M3814, Radiotherapy, and Cisplatin During the Trial

| Toxicity | Dose Modifications | | |
|---|---|---|---|
| | M3814[a] | Radiotherapy[b] | Cisplatin (only for Arm B and in the absence of institutional guidance on cisplatin dose modifications) |
| **Toxicities in Radiation Field Grade 4**<br>• Mucositis (mucosal inflammation)<br>• Radiation dermatitis | Temporarily interrupt treatment. Resume treatment once severity resolves to Grade ≤ 3. | Temporarily interrupt treatment. Resume treatment once severity resolves to Grade ≤ 3. | Temporarily interrupt treatment. Resume treatment once severity resolves to Grade ≤ 3. |
| **Systemic Toxicities**<br>• Febrile neutropenia<br>• Grade 3 thrombocytopenia with medically concerning bleeding<br>• Hematologic Toxicities: Any Grade ≥ 4 toxicity, excluding:<br>  • Grade 4 neutropenia lasting for ≤ 5 days and not associated with fever<br>  • Isolated Grade 4 lymphocytopenia without clinical correlate | Temporarily interrupt treatment. Resume treatment (at the same dose) once severity resolves to Grade ≤ 1 or Baseline. In case of a second recurrence at the same grade, permanently discontinue IMP. | No action to be taken. | Febrile neutropenia and Grade 3 thrombocytopenia with bleeding: permanent 25% dose reduction.<br>If on the day of scheduled treatment with cisplatin ANC is < 1500/mm$^3$, hold treatment until ANC ≥ 1500/mm$^3$, then treat at 100% dose.<br>If on the day of scheduled treatment with cisplatin the platelet count is < 75,000/mm$^3$, hold treatment until platelets are > 75,000/mm$^3$, then treat at 100% dose. |
| **Systemic Toxicities**<br>• Nonhematologic Toxicities<br>  • Any Grade ≥ 3 toxicity, excluding:<br>  • Diarrhea of Grade ≥ 3 (≤ 3 days duration) following adequate and optimal therapy<br>  • Nausea and vomiting of Grade ≥ 3 (≤ 3 days duration) with adequate and optimal therapy<br>  • Fatigue or headache of Grade 3 (≤ 7 days duration) following initiation of adequate supportive care<br>  • Any other single laboratory values of Grade ≥ 3 out of the normal range that have no clinical significance, and that resolve to Grade ≤ 2 with adequate measures within 7 days | Temporarily interrupt treatment. Resume treatment (at the same dose) once severity resolves to Grade ≤ 1 or Baseline. In case of a second recurrence at the same grade, permanently discontinue IMP.<br><br>In case of Grade ≥ 3 liver enzyme values, the subject must be monitored at least every 4 days until recovery to Grade ≤ 2. | No action to be taken. | Institutional guidelines. |

| | | | |
|---|---|---|---|
| • Evidence of study treatment-related hepatocellular injury for more than 3 days, such as > 5-fold elevations above the ULN of ALT or AST (CTCAE Grade 3 or 4) with or without elevation of serum total bilirubin to > 2 × ULN, without initial findings of cholestasis (elevated serum a kaline phosphatase) or other apparent clinical causality. | | | |

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CTCAE = common terminology criteria for adverse events; IMP = investigational medicinal product; RT = radiotherapy; ULN = upper limit of normal.

Note: Severity of AEs will be graded using the CTCAE (v4.03) toxicity grades.

[a] As all treatments with M3814 will be given in combination with RT, an interruption in the administration of RT would lead to an interruption in treatment with M3814.

[b] A maximum RT delay of up to and including 7 days in total is allowed within the complete treatment period. If RT and M3814 treatment have to be delayed by more than 7 days, the subject must be discontinued from M3814.

As all treatments with M3814 will be given in combination with RT, an interruption in the administration of RT would lead to an interruption in treatment with IMP. See Section 6.6.3.1 for details on handling RT treatment delays.

#### 6.3.1.1 Dosage and Administration of Concurrent Cisplatin

The currently proposed regimen for treatment-naïve subjects with SCCHN in Phase Ia (Arm B) and Phase Ib (SCCHN expansion cohort) consists of QD administration of M3814 on each RT fraction day together with the SoC (cisplatin).

On Fraction Days 1 and 31 for the 100 mg/m$^2$ dose, or weekly for the 40 mg/m$^2$ dose, cisplatin will be given according to institutional guidelines.

The timing of radiotherapy after the administration of cisplatin will also follow institutional guidelines, applicable for Phase Ia, Arm B (dose escalation) and the Arm B (SCCHN) expansion cohort only. Administration of M3814 will take place 1.5 hours (± 30 minutes) before the start of radiotherapy (see Section 6.3.1).

Body surface area (BSA) should be calculated based on a standard formula, such as the Mosteller formula [9]:

$$BSA\ (m^2) = ([Height(cm) \times Weight(kg)]/3600)^{½}$$ e.g. BSA = square root([cm×kg]/3600)

or, in inches and pounds:

$$BSA\ (m^2) = ([Height(in) \times Weight(lbs)]/3131)^{½}$$

If there is a change in body weight of at least 10 percent, the individual cisplatin dose should be recalculated. Otherwise, the initial BSA should be utilized for subsequent doses.

##### 6.3.1.1.1 Predosing Considerations for Cisplatin

Cisplatin is administered to SCCHN subjects as part of the trial. As with most cytotoxic regimens, this drug is preceded and accompanied by supportive care. General guidance on the use of cisplatin is provided. However, Investigators are referred to and need to follow the package insert, the summary of product characteristics (SmPC), and their local policies/instructions for the administration of cisplatin.

Main predosing measures for cisplatin are provided in Table 14 below and need to be assessed for the individual subject prior to the first, but also for subsequent administrations of cisplatin. Note that some measures may begin several days before actual treatment.

**Table 14 Predosing Considerations for Cisplatin**

| Issue/Indication | Recommended Steps |
|---|---|
| Pre-emesis | Follow current MASCC/ESMO[a] or NCCN[b] guidelines for chemotherapy-induced nausea and vomiting for a "high risk" regimen |
| Hydration/ nephrotoxicity | Per package insert/SmPC for cisplatin[c]. Cisplatin causes severe cumulative nephrotoxicity. A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. Adequate hydration must therefore be maintained to cause sufficient diuresis prior to, during and after treatment with cisplatin. Next to iv infusion, forced diuresis may be required and moreover subjects are to be requested to drink appropriate quantities of liquids for 24 hours after cisplatin infusion to ensure adequate urine secretion. |
| Myelosuppression/ neutropenia | Refer to the current package insert/SmPC and local guidance for modifications in dose and schedule of cisplatin[c]. Cisplatin dose should be withheld if platelet count is less than 75,000 cells/$mm^3$ or neutrophil count is less than 1500 cells/$mm^3$.<br>Primary prophylaxis with G-CSF in order to reduce the risk of febrile neutropenia (FN) is not recommended, according to ASCO[d] and ESMO guidelines. FN is defined as oral temperature >38.5°C or two consecutive readings of >38°C for 2 hours and an absolute neutrophil count <0.5 × $10^9$/L, or expected to fall below 0.5 × $10^9$/L. Secondary prophylaxis with CSFs is recommended for subjects who experienced a neutropenic complication from a previous cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease-free or OS or treatment outcome. The secondary prophylaxis should follow ASCO or ESMO or local guidelines.<br>The dosage instructions should follow the local guidelines or the ASCO or ESMO guidelines. |
| Ototoxicity/ neurotoxicity | Per package insert/SmPC for cisplatin[c]. Cisplatin is proven to be cumulative ototoxic and neurotoxic. Neurologic examination and monitoring of potential ototoxicity is to be performed prior to each cisplatin dosing and during the treatment. |

ASCO = American Society of Clinical Oncology; CSF = colony stimulating factor; ESMO = European Society for Medical Oncology; FN = febrile neutropenia; G-CSF = granulocyte-colony stimulating factor; iv = intravenous; MASCC = Multinational Association of Supportive Care in Cancer; NCCN = National Comprehensive Cancer Network; SmPC = summary of product characteristics; OS = overall survival.

[a] Annals of Oncology 21 (Supplement 5): v232–v243, 2010

[b] NCCN Guidelines Antiemesis version 2/2016

[c] https://www.medicines.org.uk/emc/medicine/25944 (Last Updated on eMC 09 January 2015)

[d] J Clin Oncol 33:3199-3212

#### 6.3.1.2 Radiotherapy

An overview of the RT technique (intensity-modulated radiotherapy [IMRT]) for dose escalation Arm B (SCCHN) in Phase Ia and both expansion cohorts in Phase Ib is given in Appendix D.

### 6.3.2 Ancillary cPoP Part

Subjects will receive a single high dose of RT (10-25 Gy) given on Lesion 1 on Day 1. On Day 2, subjects will receive a single dose of M3814 in combination with a single high dose of RT (10-25 Gy) given on Lesion 2. Subjects will fast for 1.5 hours prior to dose administration and continue to fast for 1 hour postdose. M3814 will be administered 1.5 hour (± 30 minutes) before the start of RT.

The dose of M3814 to be administered to subjects in successive cohorts of the ancillary cPoP part of the trial is shown in Table 12.

## 6.4 Assignment to Treatment Groups

All eligible subjects will be assigned to receive open label M3814. Subjects will be assigned to treatment sequentially. During dose escalation (Phase Ia) and for the first 3 NSCLC subjects in the Arm A expansion cohort (Phase Ib), the next dose level will be open for enrollment only after the DLTs in the current dose level have been fully evaluated by the SMC and a formal SMC decision to proceed to the next dose level has been documented.

## 6.5 Noninvestigational Medicinal Products to be Used

Not applicable.

## 6.6 Concomitant Medications and Therapies

All concomitant medications taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

### 6.6.1 Permitted Medicines

Any medications (other than those excluded by the clinical trial protocol) that are considered necessary for the subjects' welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

The following medications are permitted:

- Local, topical, or short-term (i.e., <7 days) of systemic corticosteroids
- Anti-infectious drugs
- Hematopoietic growth factors, if medically indicated.

The Investigator will record all concomitant medications taken by the subject and any concomitant procedures provided to the subject during the trial, from the date of signature of informed consent, in the appropriate sections of the eCRF.

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration and indication of each drug.

### 6.6.2 Prohibited Medicines

As stated in Section 5.3.2, subjects must not have received chemotherapy, immunotherapy, hormonal therapy, biologic therapy, or any other anticancer therapy or any investigational agent

within 28 days of the first dose of IMP administration (6 weeks for nitrosoureas or mitomycin C), except for subjects with rapidly growing tumors localized in the head and neck region or thorax where the treating physician cannot wait for 28 days. These therapies are also prohibited during the treatment period and up to 30 days after RT, with the exception of concurrent cisplatin in the SCCHN population (Arm B). During the treatment period and up to 30 days after RT, any other investigational agent, chemotherapy, extensive RT (involving ≥30% of bone marrow) or any other anticancer therapy (biologics or other targeted therapy) and antineoplastic steroid therapy are also prohibited (Phase Ia and Phase Ib only). Use of any investigational agent during the entire trial duration is not permitted.

Medications or herbal supplements known to be potent inhibitors or inducers of CYP3A or CYP2C19, or drugs mainly metabolized by CYP3A with a narrow therapeutic index as judged by the Investigator (and after optional consultation with the Sponsor) are prohibited (see Section 6.6.4 for details).

The solubility of M3814 is pH dependent; therefore, antacid drugs, $H_2$-blocker and PPIs might affect absorption. $H_2$-blockers or PPIs should be stopped 5 days prior to the first treatment, and avoided during the entire treatment period with IMP. Antacid drugs should not be taken 1 hour before IMP administration until 2 hours after IMP administration.

If the administration of a nonpermitted concomitant drug becomes necessary during the treatment period, e.g., due to AEs, the subject should be discontinued from the trial treatment and complete all assessments listed under the ETT visit.

See also Section 6.6.4 for details of possible drug-drug interactions with and by concomitant medication.

### 6.6.3 Other Interventions

The planning of RT will be in accordance with local practice.

**Phase Ia**: subjects will receive fractionated palliative RT (Arm A; 3 Gy x 10, 5 F/W) or fractionated RT (Arm B; 2 Gy x 33 to 35, 5 F/W) as part of curatively intended CRT (with concurrent cisplatin).

**Phase Ib**: NSCLC subjects will receive fractionated RT (2 Gy x 33, 5 F/W); SCCHN subjects will receive the same CRT regimen as in Phase Ia.

Missed fraction(s) of RT must be given at the end of the schedule to ensure that the total dose is reached. The dose of M3814 should be administered 1.5 hours (± 30 minutes) before RT. Where applicable, cisplatin should be administered according to institutional guidelines (see Section 6.3.1.1).

**Ancillary cPoP part**: subjects will receive a single high dose of RT (10-25 Gy) on Day 1 given on Lesion 1 and a single high dose of RT (10-25 Gy) on Day 2 given on Lesion 2.

#### 6.6.3.1 Radiotherapy Treatment Delay

The formal criteria for modification of RT treatment are presented in Table 13. Within this trial, a maximum delay of up to and including 7 days in total is allowed within the complete treatment period. If RT and IMP treatment have to be delayed by more than 7 days, the subject must be discontinued from IMP.


### 6.6.5 Management of Specific Adverse Events or Adverse Drug Reactions

At the current stage of development there are no known ADRs or specific AEs.

Early and late toxicities related to RT and/or M3814 will be managed according to the local institute's guidelines.

Overdose of cisplatin generally results in severe forms of normally occurring adverse reactions. Investigators are asked to check the respective information in the SmPC for further advice.

## 6.7 Packaging and Labeling of the Investigational Medicinal Product

M3814 will be packaged as boxes of CCI packs of 10 mg, 50 mg or 100 mg capsules or 50 mg tablets.

Packaging and labeling will be in accordance with all applicable local regulatory requirements and applicable Good Manufacturing Practice Guidelines.

## 6.8 Preparation, Handling, and Storage of the Investigational Medicinal Product

M3814 should be stored at the recommended temperature CCI. Any deviations from the recommended storage conditions should be immediately reported to the contact specified in the Manual of Operations, and the trial drug should not be used until authorization has been received from the Sponsor or CRO.

The Investigator or a trained designee will dispense M3814 to subjects according to their allocated dose level.

Cisplatin will be stored according to the package insert and the SmPC.

## 6.9 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring accountability for M3814, including reconciliation of drugs and maintenance of records.

- Upon receipt of M3814, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation provided by the Sponsor/CRO and returning it to the location specified. A copy will be archived for the Investigator Site File.
- IMP dispensing will be recorded on the appropriate drug accountability forms provided by the Sponsor/CRO so that accurate records will be available for verification at each monitoring visit.
- Trial site IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range
  - The inventory of IMP provided for the clinical trial and prepared at the site
  - The use of each dose by each subject
  - The disposition (including return, if applicable) of any unused IMP
  - Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for IMP prepared at the site), and the individual subject trial numbers.

The Investigator site should maintain records, which adequately document that subjects were provided the doses specified in this protocol, and that all IMPs provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. Any IMP that has been dispensed to a subject must not be redispensed to a different subject.

The Sponsor Monitor will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before authorizing their destruction by the trial site.

## 6.10 Assessment of Investigational Medicinal Product Compliance

M3814 will be administered at the site by the Investigator or designated personnel. M3814 administration, including batch numbers, kit numbers, and vial numbers must be recorded in the eCRF, as applicable.

Drug administration records will be used to assess compliance.

The Investigator is responsible for the control of drugs under investigation; adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Accountability Record, Drug Destruction Record) of the IMP, including dates, quantities, and use by subject, must be maintained.

All records and drug supplies must be available for inspection at every monitoring visit. Once the trial has been terminated and drug accountability has been satisfactorily completed by the pharmacist or trial drug preparer (or designee), the used and unused IMP (i.e., empty, partially used, and unused containers) will be released for local destruction following the internal standard operating procedures of the designated facility. The completed Drug Accountability and Drug Destruction Records will be sent to the monitor or its designee.

The site pharmacist or trial drug preparer (or designee) must maintain records of the delivery of the IMP to the trial site, the inventory at the site, the use by each subject and IMP destruction at the clinical site after drug accountability has been performed by the responsible monitor. The drug-dispensing log must be kept current, listing the identification of the subject who received IMP along with the date and quantity of IMP dispensed; it must be available for monitoring. Records shall also be maintained by the Investigator of the method of destruction (taking into account the requirements of local law), and the person who disposed of the trial drug. The temperature of the storage facilities will be monitored and documented.

After completion of the trial, any IMP distributed to the site but not administered or dispensed to or taken by the subject will be destroyed at the site. All unused medications will be carefully recorded and documented before destruction. The Investigator will ensure that the trial drug supply is not used for any purpose other than the current trial.

## 6.11 Blinding

This is an open label trial; therefore, no blinding will be performed.

## 6.12 Emergency Unblinding

Not applicable.

## 6.13 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual subject enrolled in the trial. Even if it does not meet other criteria for an SAE, any overdose must be recorded in the trial medication section of the eCRF and reported to Drug Safety in an expedited manner using the SAE Report Form, and following the procedure in Section 7.4.1.4.

There is no established treatment for overdose with M3814. The Investigator should use clinical judgment to manage any overdose considering the presenting symptoms and standard evaluation results.

## 6.14 Medical Care of Subjects after End of Trial

After a subject has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial site's SoC and generally accepted medical practice and depending on the subject's individual medical needs.

# 7 Trial Procedures and Assessments

## 7.1 Schedule of Assessments

Prior to performing any trial assessments that are not part of routine medical care for the subject, the Investigator will obtain written informed consent as described in Section 9.2.

Complete schedules of assessments for Phase Ia (Arm A – Capsule and Tablet), Phase Ib – first 3 subjects (Arm A, NSCLC cohort), Phase Ib (Arm A, NSCLC cohort), Phase Ia (Arm B, SCCHN cohort), Phase Ib (Arm B, SCCHN cohort) and ancillary cPoP parts are provided in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6 and Table 7, respectively. During RT, no visit window will be allowed.

Every effort should be made to perform assessments as close as possible to the scheduled time points.

### 7.1.1 Screening Period (Day -21 to Day -1)

Based on the findings obtained during the Screening Period, the Investigator will decide whether the subject is eligible for the trial. Scheduled screening assessments in all subjects are as follows:

- Provision of written informed consent for the trial and PGx analysis and review of inclusion and exclusion criteria
- Documentation of demographics, relevant medical history, and concomitant medications

- Safety laboratory (hematology, serum chemistry, urinalysis, coagulation and serum β-human chorionic gonadotropin [HCG] pregnancy test [if applicable])
- Infection screen. Hepatitis B and C testing to be performed unless obtained within 3 months prior to Screening. Screening for HIV will be performed according to local practice and local regulatory guidance
- Evaluation of human papillomavirus status in tumor material by immunohistochemistry (Phase Ia, Arm B and Phase Ib, Arm B expansion cohort only)
- Audiogram, as needed according to local guidelines (Phase Ia, Arm B and Phase Ib, Arm B expansion cohort only)
- Assessment of vital signs (blood pressure and heart rate), body weight, and height, body temperature (height measured at Screening only)
- Assessment of AEs
- Tumor evaluation by radiographic or other modality (RECIST v1.1) (Phase Ia and Phase Ib only). Baseline tumor evaluation can be up to 28 days old when treatment starts
- ECOG PS
- 12-lead ECG including the Fridericia-corrected QT interval (QTcF)
- Physical examination
- Clinical examination of bleeding (including petechiae, in skin, in the sclera of the eye, oral mucosa) (Phase Ia and Phase Ib only).
- In case of clinical signs of esophagitis, an esophageal endoscopy must be performed, if the radiation fields involve the esophagus.

Ancillary cPoP part of the trial only:

- Evaluation of all tissues in the RT area
- Local tumor assessment (in irradiated lesions) by clinical exam or imaging according to RECIST v1.1 (only applicable for additional cohorts of M3814 [CCI formulation]).

### 7.1.2 Treatment Period

#### 7.1.2.1 Phase Ia Part: Arm A and Arm B (Fraction Days 1 to 10)

Eligible subjects will receive M3814 during the period in which RT is given.

The following assessments will be performed on Fraction Days 1, 6 and 10; if Fraction Day 10 is on a Friday, PK, CCI safety laboratory, and urinalysis sampling must be done on Fraction Day 9:

- Review of inclusion and exclusion criteria (Fraction Day 1 only)
- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight (see Section 7.4.4 for details)

- Physical examination
- Clinical examination of bleeding (including petechiae, in skin, in the sclera of the eye, oral mucosa)
- Evaluation of all tissues in the RT area (Fraction Day 6 and 10 only)
- ECOG PS (Fraction Day 10 only)
- Assessment of AEs
- Documentation of concomitant medications
- Safety laboratory (hematology, serum chemistry and coagulation)
- Urinalysis (Fraction Day 10 only)
- 12-lead ECG including QTcF (Fraction Day 1 and 10)
- Collection of PK blood samples
- Availability of archival tumor material, either as a block or slides. If no archival material is available then a fresh biopsy should be taken

CCI [redacted]

The following assessments will be performed on Fraction Day 2:

- Collection of PK blood samples (predose)

CCI [redacted]

#### 7.1.2.2 Phase Ia Part: Arm B (SCCHN) (Fraction Days 16 to 31)

Eligible subjects will receive M3814 during the period in which RT is given.

The following assessments will be performed on Fraction Days 16, 21, 26, 31, and last FD/ETT

- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight (see Section 7.4.4 for details)
- Physical examination
- Clinical examination of bleeding (including petechiae, in skin, in the sclera of the eye, oral mucosa)
- Evaluation of all tissues in the RT area
- ECOG PS (last Fraction Day only)
- Assessment of AEs
- Documentation of concomitant medications

- Safety laboratory (hematology, serum chemistry and coagulation)
- Urinalysis (Fraction Day 16 and last Fraction Day only)
- 12-lead ECG including QTcF

#### 7.1.2.3 Phase Ib Part: Arm A (NSCLC) Expansion Cohort (Fraction Days 1 to 33)

Eligible subjects will receive M3814 during the period in which RT is given.

The following assessments will be performed on Fraction Days 1, 6 (first 3 subjects only), 10, 16, 21, 26 and 33; if Fraction Day 10 is on a Friday, PK, PD, and safety laboratory sampling must be done on Fraction Day 9:

- Review of inclusion and exclusion criteria (Fraction Day 1 only)
- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight (see Section 7.4.4 for details)
- Physical examination
- Clinical examination of bleeding (including petechiae, in skin, in the sclera of the eye, oral mucosa)
- Evaluation of all tissues in the RT area (not performed on Fraction Day 1)
- ECOG PS (Fraction Day 33 only)
- Assessment of AEs
- Documentation of concomitant medications
- Safety laboratory (hematology, serum chemistry and coagulation)
- Urinalysis (Fraction Days 10 [first 3 subjects only], 16, and 33 only)
- 12-lead ECG including QTcF (Fraction Day 1 and 10)
- Collection of PK blood samples (Fraction Days 1 and 10 only)
- Availability of archival tumor material, either as a block or slides. If no archival material is available then a fresh biopsy should be taken

CCI [redacted]

The following assignments will be performed on Fraction Day 2 (first 3 subjects only):

- Collection of PK blood samples (predose)

CCI [redacted]

### 7.1.2.4 Phase Ib Part: Arm B (SCCHN) Expansion Cohort (Fraction Days 1 to Last Fraction Day)

Eligible subjects will receive M3814 during the period in which CRT is given.

The following assessments will be performed on Fraction Days 1, 6, 10, 16, 21, 26, 31 and the last Fraction Day (33 to 35); if Fraction Day 10 is on a Friday, PK, CCI and safety laboratory sampling must be done on Fraction Day 9:

- Review of inclusion and exclusion criteria (Fraction Day 1 only)
- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight (see Section 7.4.4 for details)
- Physical examination
- Clinical examination of bleeding (including petechiae, in skin, in the sclera of the eye, oral mucosa)
- Evaluation of all tissues in the RT area (not performed on Fraction Day 1)
- ECOG PS (last Fraction Day only)
- Assessment of AEs
- Documentation of concomitant medications
- Safety laboratory (hematology, serum chemistry and coagulation)
- Urinalysis (Fraction Day 16 and last Fraction Day only)
- 12-lead ECG including QTcF
- Collection of PK blood samples (Fraction Days 1 and 10 only)
- Availability of archival tumor material, either as a block or slides. If no archival material is available then a fresh biopsy should be taken

CCI [redacted]

### 7.1.2.5 Ancillary cPoP Part

Eligible subjects will receive a single high dose of RT given on Lesion 1 on Day 1, and on Day 2, will receive M3814 with a single high dose of RT given on Lesion 2.

For logistical reasons (handling and sending materials), Day 1 must be on a Wednesday or earlier.

The following assessments will be performed on Day 1 and Day 2:

- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight (see Section 7.4.4 for details).

- Evaluation of all tissues in the RT area (Day 2 only)
- Assessment of AEs
- Documentation of concomitant medications
- Tumor biopsy:
    - Day 1: baseline biopsy to be taken any time prior to RT for both lesions (Screening to Day 1) and 2-4 hours after RT for Lesion 1
    - Day 2: to be taken 2-4 hours after RT for Lesion 2.

CCI [redacted]

### 7.1.3 Follow-up Period

#### 7.1.3.1 DLT Period: Phase Ia, Arm A

The following assessments will be performed on PTD 8 and 15:

- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight
- Physical examination
- Clinical examination of bleeding (including petechiae, in skin, in the sclera of the eye, oral mucosa)
- Evaluation of all tissues in the RT area
- ECOG PS
- Assessment of AEs
- Documentation of concomitant medications
- Safety laboratory (hematology, serum chemistry and coagulation)
- Urinalysis.

#### 7.1.3.2 DLT Period/Short-term Safety Follow-up: Phase Ia, Arm B and First 3 Subjects in Phase Ib (Arm A Expansion Cohort in NSCLC)

The following assessments will be performed on PTD 7, 14, 21, 28 and 35 (Phase Ia, Arm B) or on PTD 8, 15, 22 and 37 (first 3 subjects in Phase Ib, Arm A):

- Serum β-HCG pregnancy test (if applicable and only PTD 28 [Phase Ia, Arm B] or PTD 22 [first 3 subjects in Phase Ib, Arm A])
- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight
- Physical examination
- Clinical examination of bleeding (including petechiae, in skin, in the sclera of the eye, oral mucosa)
- Evaluation of all tissues in the RT area
- ECOG PS
- Assessment of AEs
- Documentation of concomitant medications
- Safety laboratory (hematology, serum chemistry and coagulation)
- Urinalysis.

#### 7.1.3.3 Short-term Safety Follow-up: Phase Ia, Arm A and Phase Ib

The following assessments will be performed on PTD 22 and 30 in Phase Ia (Arm A) and on PTD 8, 15, 22 and 30 in Phase Ib:

- Serum β-HCG pregnancy test (if applicable and only PTD 30)
- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight
- Physical examination
- Clinical examination of bleeding (including petechiae, in skin, in the sclera of the eye, oral mucosa)
- Evaluation of all tissues in the RT area
- ECOG PS (PTD 30 only)
- Assessment of AEs
- Documentation of concomitant medications
- Safety laboratory (hematology, serum chemistry and coagulation)
- Urinalysis (PTD 30 only).

### 7.1.3.4 Mid-term Safety Follow-up: Phase Ia and Phase Ib

The mid-term safety follow-up will be performed on PTD 84. To evaluate signs of RT-induced toxicity on normal surrounding tissues, the following assessments were performed:

- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight (Phase Ia only)
- Physical examination
- 12-lead ECG including QTcF (Arm B SCCHN cohort only)
- ECOG PS
- Evaluation of all tissues in the RT area
- Evaluation of ongoing TEAEs

### 7.1.3.5 Long-term Safety Follow-up: Phase Ia and Phase Ib

The following assessments will be performed for all subjects, excluding subjects in the ancillary cPoP part of the trial, on PTD 42, 126, 168, and 180, (Phase Ia and Phase Ib), and on PTD 270 and 365 (Phase Ib only):

- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight
- Physical examination
- 12-lead ECG including QTcF (Arm B SCCHN cohort only)
- ECOG PS
- Evaluation of all tissues in the RT area
- Evaluation of ongoing TEAEs
- Tumor assessment according to RECIST v1.1, only required if subject has not started a new antitumor treatment. If a new treatment is started, the date (and regimen) must be reported in eCRF.

The following assessments will be performed on PTD 210 and 312:

- Evaluation of long term RT toxicity (subject called by phone).

### 7.1.3.6 Survival Follow-up: Phase Ia and Phase Ib

The following assessments will be performed on PTD 270 and 365 (EOT) for patients in Phase Ia, Arm A:

- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight. Only required for Phase Ia if subject has not started a new antitumor treatment
- Physical examination
- ECOG PS

- Evaluation of all tissues in the RT area
- Evaluation of ongoing TEAEs
- Tumor assessment according to RECIST v1.1. Only required for Phase Ia if subject has not started a new antitumor treatment.

For all patients, the survival follow-up period will continue until 12 months after the last subject has stopped RT/CRT (defined as end of trial; see Section 5.7). After completion of the visit on PTD 365, all subjects will be followed for survival every 3 months via a phone call until the end of the trial.

#### 7.1.3.7 Follow-up for the Ancillary cPoP Part of the Trial

The following assessments will be performed on Day 10 and Day 32 (8 and 30 days after end of treatment):

- Assessment of vital signs (blood pressure, heart rate, and body temperature), body weight (Day 10 only)
- Evaluation of all tissues in RT area
- Assessment of AEs (local tolerability 30 days after last trial drug administration)
- Documentation of concomitant medications (only at Day 10)
- Safety laboratory (hematology, serum chemistry and coagulation)
- Local tumor assessment (in irradiated lesions) by clinical exam or imaging according to RECIST v1.1 (only at Day 10 and only applicable for additional cohorts of M3814 [CCI formulation]).

### 7.1.4 Discontinuation/End of Trial

For the Phase Ia and Ib parts, all subjects who discontinue IMP must undergo a full safety evaluation at the time of discontinuation. The assessments specified for the ETT visit should be performed (see Table 1 [Phase Ia – Arm A capsule cohorts], Table 2 [Phase Ia – Arm A tablet cohorts], Table 3 [first 3 subjects in Phase Ib – Arm A, NSCLC cohort], Table 4 [Phase Ib – Arm A, NSCLC cohort], Table 5 [Phase Ia – Arm B, SCCHN cohort] and Table 6 [Phase Ib – Arm B, SCCHN cohort] for details).

An EOT visit will also be performed on PTD 365, or if the subject withdraws prior to PTD 365. All assessments must be done as planned for the EOT visit, see Sections 7.1.3.5 and 7.1.3.6.

## 7.2 Demographic and Other Baseline Characteristics

The assessments and procedures described in this section must be performed during the Screening Period.

### 7.2.1 Demographic Data

The following demographic data will be recorded:

- Subject identifier
- Date of birth
- Sex
- Race
- Ethnicity

### 7.2.2 Tumor History

The following information will be documented and verified at the Screening visit for each subject:

- All therapy used for prior treatment of the tumor (including surgery, RT, chemotherapy, immunotherapy, and hormonal or biologic therapy)
- Current cancer signs and symptoms and side effects from current and/or previous anticancer treatments
- Date of diagnosis and histology, whenever possible
- Grading and staging of the tumor
- Date of the first occurrence of disease and the date of progression after the first, second, and any subsequent treatment failure.
- Human papillomavirus evaluation in SCCHN tumor material (for Phase Ia, Arm B and Phase Ib, SCCHN expansion cohort only)

### 7.2.3 Medical History and Previous and Concomitant Medication

To determine the subject's eligibility for the trial, relevant medical history of each subject will be collected and documented during screening that will include the following:

- Past and concomitant nonmalignant diseases and treatments
- All medications taken and procedures carried out within 21 days prior to screening.

For trial entry, all subjects must fulfill all inclusion criteria described in Section 5.3.1 and none of the exclusion criteria described in Section 5.3.2.

### 7.2.4 Vital Signs and Physical Examination

Vital signs, including body temperature, heart rate and blood pressure (after 5 minutes rest), will be recorded at trial entry.

A complete physical examination (including general appearance, dermatological, head/neck, pulmonary, cardiovascular, gastrointestinal, genitourinary, lymphatic, musculoskeletal system,

extremities, eyes [inspection and vision control], nose, throat, and neurologic status) will be performed and the results documented.

Clinical examination of bleeding (including petechiae, in skin, in the sclera of the eye, oral mucosa) will be performed.

The ECOG PS will be documented during the Screening Period.

Body weight and height will be recorded.

### 7.2.5 CT or Magnetic Resonance Imaging Scans for Tumor Assessment

An enhanced CT scan or enhanced magnetic resonance imaging (MRI) of the tumor will be performed prior to the beginning of trial treatment to document the baseline status of the tumor using RECIST v1.1 (Appendix B). Baseline tumor evaluation can be up to 28 days old when treatment starts.

### 7.2.6 Cardiac Assessments

Triplicate 12-lead ECGs will be recorded locally at screening (predose) after the subject has been in a supine position breathing quietly for at least 5 minutes and postdose. The ECG results will be used to evaluate the heart rate, atrial ventricular conduction, QR and QT intervals (including QTcF), and possible arrhythmias.

### 7.2.7 Clinical Laboratory Tests

Blood samples will be collected locally at screening for clinical laboratory parameter evaluations. These clinical laboratory test results will serve not only as the baseline values for subsequent safety clinical laboratory evaluations during the trial but also as verification that each enrolled subject fulfills all the trial entry criteria and does not meet any of the trial exclusion criteria for laboratory parameters as listed in Section 5.3.2. Detailed description of laboratory assessments is provided in Section 7.4.3.

## 7.3 Efficacy Assessments

### 7.3.1 Tumor Response Assessment

Tumor response will be evaluated according to RECIST v1.1 (see Appendix B).

The tumor response assessment will be performed as listed according to the schedules of assessments (Table 1 [Phase Ia – Arm A capsule cohorts], Table 2 [Phase Ia – Arm A tablet cohorts], Table 3 [first 3 subjects in Phase Ib – Arm A, NSCLC cohort], Table 4 [Phase Ib – Arm A, NSCLC cohort], Table 5 [Phase Ia – Arm B, SCCHN cohort] and Table 6 [Phase Ib – Arm B, SCCHN cohort]). This should include a complete assessment of all target and nontarget lesions for subjects with solid tumors. This assessment will be performed by CT or MRI.

In general, lesions detected during screening need to be followed using the same methodology and preferably the same equipment at subsequent tumor assessment visits.

For the ancillary cPoP part of the trial (only applicable for additional cohorts of M3814 [CCI formulation]): The local tumor response assessment in irradiated lesions will be performed as listed according to the schedule of assessments (Table 7). Local tumor response in irradiated lesions will be evaluated according to RECIST v1.1 (see Appendix B). This assessment will be performed following the institutional practices, either by clinical exam or imaging. Lesions assessed during screening need to be followed by the same technique and methodology of assessment at the subsequent tumor assessment visit on Day 10. The cutaneous and subcutaneous lesions should also be documented by color photography (including a caliper or scale) at Baseline and on Day 10.

## 7.4 Assessment of Safety

The safety profile of M3814 will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings including vital signs and monitoring for bleeding, laboratory tests, ECOG PS, and 12-lead ECGs.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent up to 12 months after RT completion. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3.

### 7.4.1 Adverse Events

#### 7.4.1.1 Adverse Event Definitions

**Adverse Event**

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

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute (NCI)-CTCAE, v4.03 (publication date: 14 June 2010), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If a particular AE severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE (v4.03) definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death.

According to the Sponsor's convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

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

Investigators must also systematically assess the causal relationship of AEs to the trial treatment using the following definitions. Decisive factors for the assessment of causal relationship of an AE to M3814/RT/CRT include temporal relationship between the AE and M3814/RT/CRT, known side effects of M3814/RT/CRT, medical history, concomitant medication, course of the underlying disease, trial procedures.

**Unrelated:** Not reasonably related to M3814/RT/CRT treatment. AE could not medically (pharmacologically/clinically) be attributed to M3814/RT/CRT treatment under study in this clinical trial protocol. A reasonable alternative explanation must be available.

**Related:** Reasonably related to M3814/RT/CRT treatment. AE could medically (pharmacologically/clinically) be attributed to M3814/RT/CRT treatment under study in this clinical trial protocol.

**Abnormal Laboratory Findings and Other Abnormal Investigational Findings**

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

**Serious Adverse Events**

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.).

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE as described in Section 7.4.1.4.

**Events that Do Not Meet the Definition of an SAE**

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (for example, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

**Events Not to Be Considered as AEs/SAEs**

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are NOT to be considered AEs.

**AEs/SAEs Observed in Association with Disease Progression**

Progression of the disease/disorder being studied, assessed by measurement of lesions on radiographs or other methods, as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the patient's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the adverse event reporting period (as defined in Section 7.4.1.3).

**Adverse Events of Special Interest for Safety Monitoring**

Not yet defined.

**Dose Limiting Toxicities**

Each DLT (as defined in Section 7.4.1.5), regardless of seriousness must be immediately recorded in the eCRF. In addition, serious DLTs have to reported in an expedited manner as for SAEs as described in Section 7.4.1.4.

### 7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be documented additionally and reported using the appropriate form as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates [and times when it is important to assess the time of AE onset relative to the recorded treatment administration time]), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented. If an AE constitutes a DLT this has to be documented accordingly.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

### 7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent) and continues through the trial's post-treatment follow-up period up to PTD 365.

A TEAE is defined as any AE that occurs from the day of first dose of M3814 (regardless of pretreatment or post-treatment on first dosing day), through Day 30 after the end of RT.

Any SAE assessed as related to M3814 must be reported whenever it occurs irrespective of the time elapsed since the last administration of M3814.

### 7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities

**Serious Adverse Events**

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 hours after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter.

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant medication). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report and autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the CRO's Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

**Dose Limiting Toxicities**

Each event meeting the criteria of a DLT (see Section 7.4.1.5) must be recorded in the eCRF within 24 hours after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs as outlined above.

### 7.4.1.5 Dose Limiting Toxicities

A DLT is defined as any Grade $\geq 3$ nonhematologic AE or any Grade $\geq 4$ hematologic AE (according to NCI-CTCAE version 4.03) that is related to any of the study treatments and occurs during the DLT period of 5 weeks (Phase Ia, Arm A) or 12 weeks (Phase Ia, Arm B and Phase Ib, first 3 subjects in the expansion cohort of Arm A [NSCLC]) after the first dose of M3814.

A DLT must be confirmed by the SMC.

In addition, the following are considered DLTs:

1. Grade 3 thrombocytopenia with medically concerning bleeding

2. Febrile neutropenia
3. Any toxicity or study treatment-related TEAE that, in the opinion of the SMC, is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk
4. Any toxicity related to study treatments that causes the subject to receive less than 80% of the planned RT dose
5. Any toxicity related to study treatments leading to an interruption of RT longer than 1 week in Arm B
6. Evidence of study treatment-related hepatocellular injury for more than 3 days, such as > 5-fold elevations above the ULN of ALT or AST (CTCAE Grade 3 or 4) with or without elevation of serum total bilirubin to $> 2 \times$ ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) or other apparent clinical causality.

The following study treatment-related AEs are exceptions to the above mentioned DLT definition and are **not** considered to be DLTs:

1. Mucositis (mucosal inflammation), including oral mucositis (stomatitis) of Grade $\geq 3$ lasting for $\leq 4$ weeks after completion of the study treatments
2. Stomatitis associated toxicities (e.g., swallowing dysfunction [odynophagia, dysphagia], decreased appetite or weight loss due to difficulty or painful swallowing) of Grade $\geq 3$ lasting for $\leq 4$ weeks after completion of the study treatments
3. Diarrhea of Grade $\geq 3$ ($\leq 3$ days duration) following adequate and optimal therapy
4. Nausea and vomiting of Grade $\geq 3$ ($\leq 3$ days duration) with adequate and optimal therapy
5. Radiation dermatitis and associated toxicities of Grade $\geq 3$ lasting for $\leq 4$ weeks after completion of the study treatments
6. Neutropenia of Grade 4 lasting for $\leq 5$ days and not associated with fever
7. Isolated Grade 4 lymphocytopenia without clinical correlate
8. Fatigue or headache of Grade 3 ($\leq 7$ days duration) following initiation of adequate supportive care
9. Any other single laboratory values of Grade $\geq 3$ out of the normal range that have no clinical significance, and that resolve to Grade 2 or less with adequate measures within 7 days.

The duration of feeding tube (FT) use (nasogastric tube, percutaneous endoscopic gastrostomy) should not define the severity of the toxicity (e.g., severe swallowing dysfunction, nausea, vomiting). A careful evaluation of the subject's symptoms by the Investigator at each visit is required in order to identify subjects who are FT dependent (e.g., subjects who refuse/avoid swallowing, etc).

- In the event of severe swallowing dysfunction (Grade ≥ 3 dysphagia or odynophagia) that requires FT placement and resolves to Grade ≤ 2 prior to the end of 4 weeks after completing study treatments, if the FT is still in place for other reasons then dysphagia or odynophagia will not be considered a DLT.
- In the event of Grade 3 nausea or Grade ≥ 3 vomiting that requires FT placement and resolves to Grade ≤ 2 within 3 days, if the FT is still in place for other reasons then nausea or vomiting will not be considered a DLT.

The SMC may identify as a DLT, any ADR that impairs daily function, or abnormality occurring in subjects treated with M3814 at any time during the trial including in-field late radiation toxicities.

Subjects who discontinue treatment with M3814 because of a DLT should not be re-exposed to the trial drug but ongoing RT can continue.

Subjects who do not complete the DLT observation period for reasons other than a DLT will be replaced.

#### 7.4.1.6 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor/designee will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

#### 7.4.1.7 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the PTD 365 visit. All SAEs ongoing at the EOT visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

### 7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the SAE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child/Fetus AE Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor/designee must be notified without delay and the subject must be followed as mentioned above.

### 7.4.3 Clinical Laboratory Assessments

It is essential that the Sponsor or designee be provided with a list of laboratory normal ranges before shipment of trial drug. Any change in laboratory normal ranges during the trial will additionally be forwarded to the Sponsor or designee.

Results must be available prior to the first dose of IMP. The report of the results must be retained as part of the subject's medical record or source documents.

Blood and urine samples will be collected for the following clinical laboratory tests, following the timing noted in the Schedules of Assessments (Table 1, Table 2, Table 3, Table 4, Table 5, Table 6 and Table 7 for Phase Ia [Arm A capsule cohort], Phase Ia [Arm A tablet cohort], Phase Ib – first 3 subjects [Arm A, NSCLC cohort], Phase Ib [Arm A, NSCLC cohort], Phase Ia [Arm B, SCCHN cohort], Phase Ib [Arm B, SCCHN cohort] and ancillary cPoP parts, respectively). All samples should be clearly identified. Urinalysis (sediment and protein content) will also be performed at specified time points.

**Table 15 Required Laboratory Safety Tests**

| Serum Chemistry | Hematology |
|---|---|
| Albumin | White blood cells and differential count |
| Alkaline phosphatase | Hemoglobin |
| Alanine aminotransferase | Hematocrit |
| Aspartate aminotransferase | Red blood cells |
| Blood urea nitrogen | Mean corpuscular volume |
| Calcium | Mean corpuscular hemoglobin |
| Creatine phosphokinase | Mean corpuscular hemoglobin concentration |
| Creatinine | Reticulocytes |
| | Platelet count |
| Gamma glutamyltransferase | Absolute lymphocyte count |
| Glucose | Absolute neutrophil count |
| Lactate dehydrogenase | |
| Magnesium | **Coagulation** |
| Phosphorous | International normalized ratio |
| Potassium | Activated partial thromboplastin time |
| Sodium | |
| Total bilirubin | **Infection screen** |
| Total protein | Hepatitis B |
| Uric acid | Hepatitis C |
| β-human chorionic gonadotropin in female subjects (if applicable) | Human immunodeficiency virus (according to local practice and local regulatory guidance) |

For women of childbearing potential, pregnancy testing (serum β-HCG) will be performed during the Screening Period and at the visits specified in the Schedule of Assessments. Subjects after menopause (age-related amenorrhea ≥ 12 consecutive months) or subjects who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

Details on the blood volume to be drawn from each subject during the trial are presented in a separate laboratory document.

For the Phase Ia and Ib parts, including the blood volume drawn for research purposes (PK, PD markers, and PGx) and safety assessments, the total volume of blood drawn from each subject during the Screening Period (including predose) will be approximately 61 mL. During the treatment period, DLT period and Short-term Safety Follow-up (excluding predose), the total

volume of blood drawn from each subject will be approximately 138 mL (Phase Ia, Arm A), 186 mL (first 3 subjects in Phase Ib, Arm A expansion cohort [NSCLC]), 172 mL (Phase Ib, Arm A expansion cohort [NSCLC]), 210 mL (Phase Ia, Arm B) and 184 mL (Phase Ib, Arm B expansion cohort [SCCHN]). The total volume of blood drawn from each subject in the ancillary cPoP part of the trial, including blood sampling for markers, is approximately 73 mL.

### 7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Vital signs (blood pressure, heart rate, and body temperature), body weight, and ECOG PS will be measured as described in the Schedule of Assessments: (Table 1, Table 3, Table 4, Table 5, Table 6 and Table 7 for Phase Ia [Arm A], Phase Ib – first 3 subjects [Arm A, NSCLC cohort], Phase Ib [Arm A, NSCLC cohort], Phase Ia [Arm B, SCCHN cohort], Phase Ib [Arm B, SCCHN cohort] and ancillary cPoP parts, respectively). If possible, diastolic/systolic blood pressure should be taken on the same arm at each visit.

Physical examinations will be obtained predose and postdose. Vital signs (blood pressure, heart rate, and body temperature) assessments should be performed predose and 2 to 3 hours postdose. Body weight will be measured predose only. 12-lead ECGs (in triplicate after the subject has been supine for at least 5 minutes) should be performed predose and 2 to 3 hours postdose on Fraction Day 1, and 2 hours postdose on Fraction Day 10.

In the ancillary cPoP part of the trial, vital signs and body weight should be measured predose.

## 7.5 Pharmacokinetics

### 7.5.1 Sample Collection

Details of PK blood sample collection and processing procedures, storage, and transportation will be summarized in the laboratory specifications document.

For details of PK blood sampling time points in the Phase Ia, Phase Ib, and ancillary cPoP parts of the trial, see Table 9.

Pharmacokinetic sampling should be performed within ± 15 minutes of the first 30 minute postdose sample collections, and within ± 30 minutes for subsequent sampling at each sampling day. The predose sample should be taken within 1 hour before dosing at each sampling day. Approximately 2 mL of blood should be collected at each scheduled time. The drug administration, actual date and exact blood sampling time must be recorded.

The SMC may modify the PK sampling schedule based upon PK information collected during the trial. The SMC is not expected to increase the overall amount of blood to be collected for PK sampling.

## 7.5.2 Pharmacokinetic Calculations

### 7.5.2.1 Non Compartmental Analysis

Capsule formulation:

The following PK parameters will be calculated for the M3814 concentration data obtained on Fraction Day 1 and Fraction Day 10 (if Fraction Day 10 is on a Friday, then these evaluations will be done on Fraction Day 9) in the Phase Ia part using noncompartmental analysis approaches as appropriate:

- $C_{max}$
- Time to reach maximum observed concentration ($t_{max}$)
- AUC over the dosing interval after multiple dosing ($AUC_{\tau}$) (Fraction Day 10 only)
- AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-t}$) (Fraction Day 1 only) AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$, Fraction Day 1 and only if meaningful on Fraction Day 10)
- Apparent terminal half-life ($t_{1/2}$)
- Oral clearance (CL/f) (Fraction Day 1 only)
- Oral clearance at steady state (CLss/f) (Fraction Day 10 only)
- Apparent volume of distribution during terminal phase (Vz/f) (Fraction Day 1 only)
- Apparent volume of distribution at steady state (Vss/f) (Fraction Day 10 only)
- Accumulation ratio for AUC ($R_{acc}$[AUC]) (Fraction Day 10 only)
- Accumulation ratio for $C_{max}$ ($R_{acc}$[$C_{max}$]) (Fraction Day 10 only).

Tablet formulation:

The following PK parameters will be calculated for the M3814 concentration data obtained on Fraction Day 1, 6 (if a patient does not start treatment on a Monday, then "FD 6" becomes the FD that is closest to a Monday. Therefore, there will be a wash-out of M3814 over the weekend) and Fraction Day 10 (if Fraction Day 10 is on a Friday, then these evaluations will be done on Fraction Day 9) in the Phase Ia part using noncompartmental analysis approaches as appropriate:

- $C_{max}$
- Time to reach maximum observed concentration ($t_{max}$)
- AUC over the dosing interval after multiple dosing ($AUC_{\tau}$) (Fraction Day 10 only)
- AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-t}$) (Fraction Day 1 and Fraction Day 6) AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$, Fraction Day 1 and Fraction Day 6, and only if meaningful on Fraction Day 10)
- Apparent terminal half-life ($t_{1/2}$)

- Oral clearance (CL/f) (Fraction Day 1 and Fraction Day 6 only)
- Oral clearance at steady state (CLss/f) (Fraction Day 10 only)
- Apparent volume of distribution during terminal phase (Vz/f) (Fraction Day 1 and Fraction Day 6 only)
- Apparent volume of distribution at steady state (Vss/f) (Fraction Day 10 only)
- Accumulation ratio for AUC ($R_{acc}$[AUC]) (Fraction Day 10 only)
- Accumulation ratio for $C_{max}$ ($R_{acc}$[$C_{max}$]) (Fraction Day 10 only).

Additional PK parameters may be calculated.

Plasma concentration of M3814 will be determined by a Liquid chromatography-tandem mass spectrometry method.

#### 7.5.2.2 Population PK Analysis and Simulation

**Population pharmacokinetic**

Objectives of the population PK analysis will be:

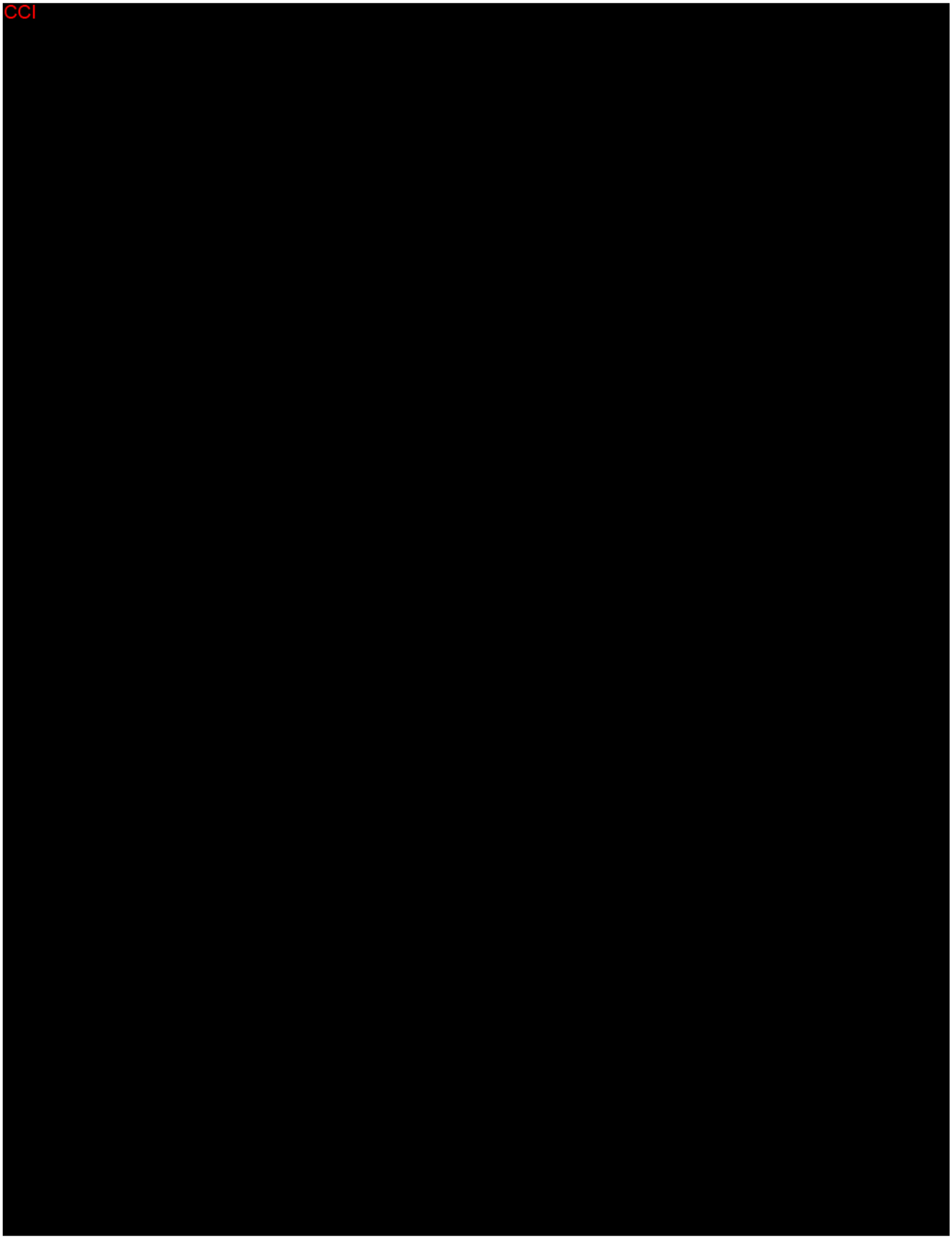
- Identification of population PK model of M3814
- Estimation of typical population PK parameters of M3814 as clearances, central and peripheral volumes, etc.
- Estimation of the variability of the population PK parameters
- Identification of additional covariates, such as demographics, comedication or medical history, that are significant predictors of PK variability, RT dose.

**Simulation**

If requested, simulation of an alternative dosing regimen will be performed in order to achieve a certain target.

The population analysis will be conducted with software package NONMEM (version 7.2.0), while the simulations will be performed with either NONMEM or SIMULX software.

CCI [redacted]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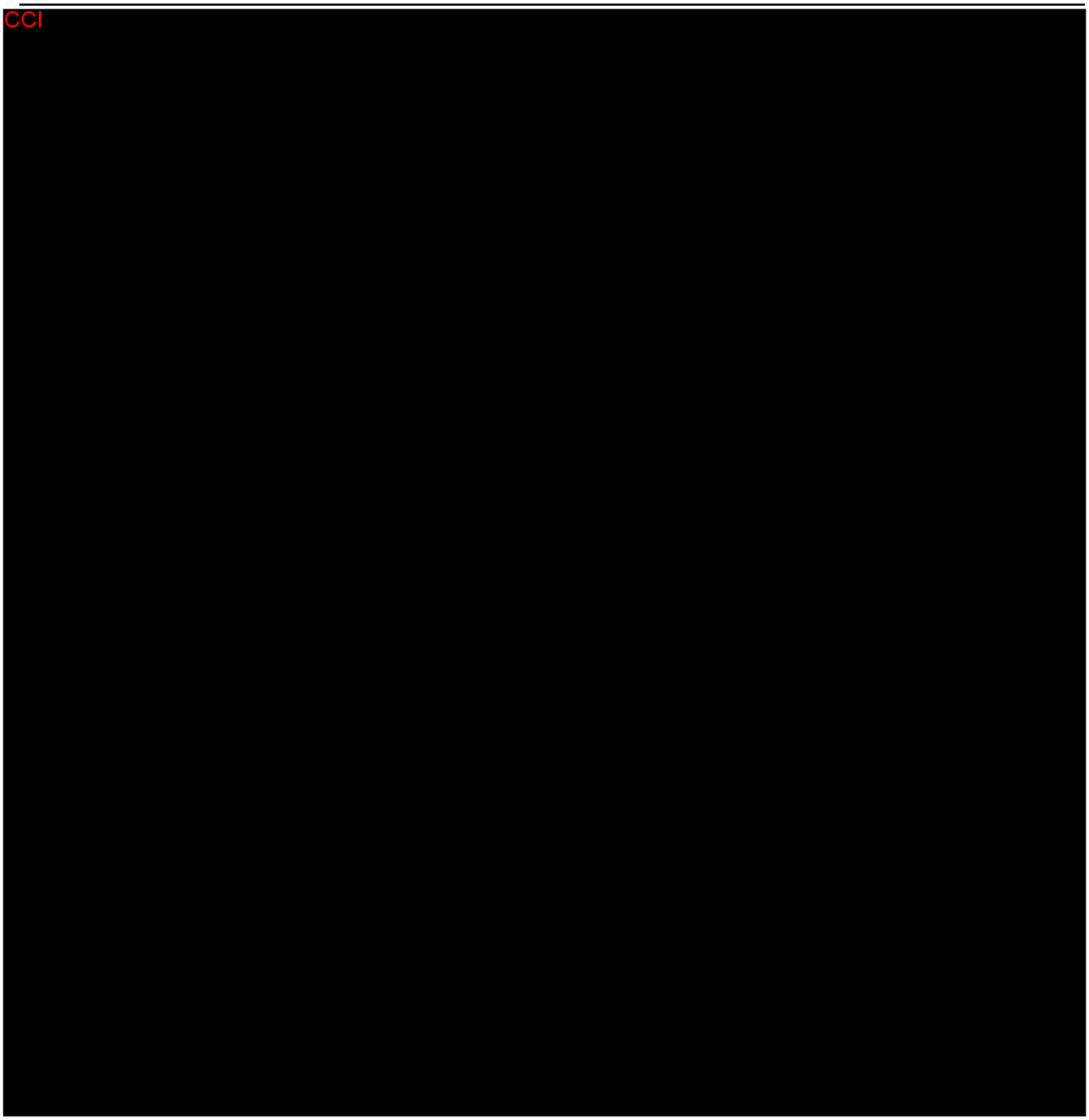
## 7.7 Other Assessments

Not applicable.

# 8 Statistics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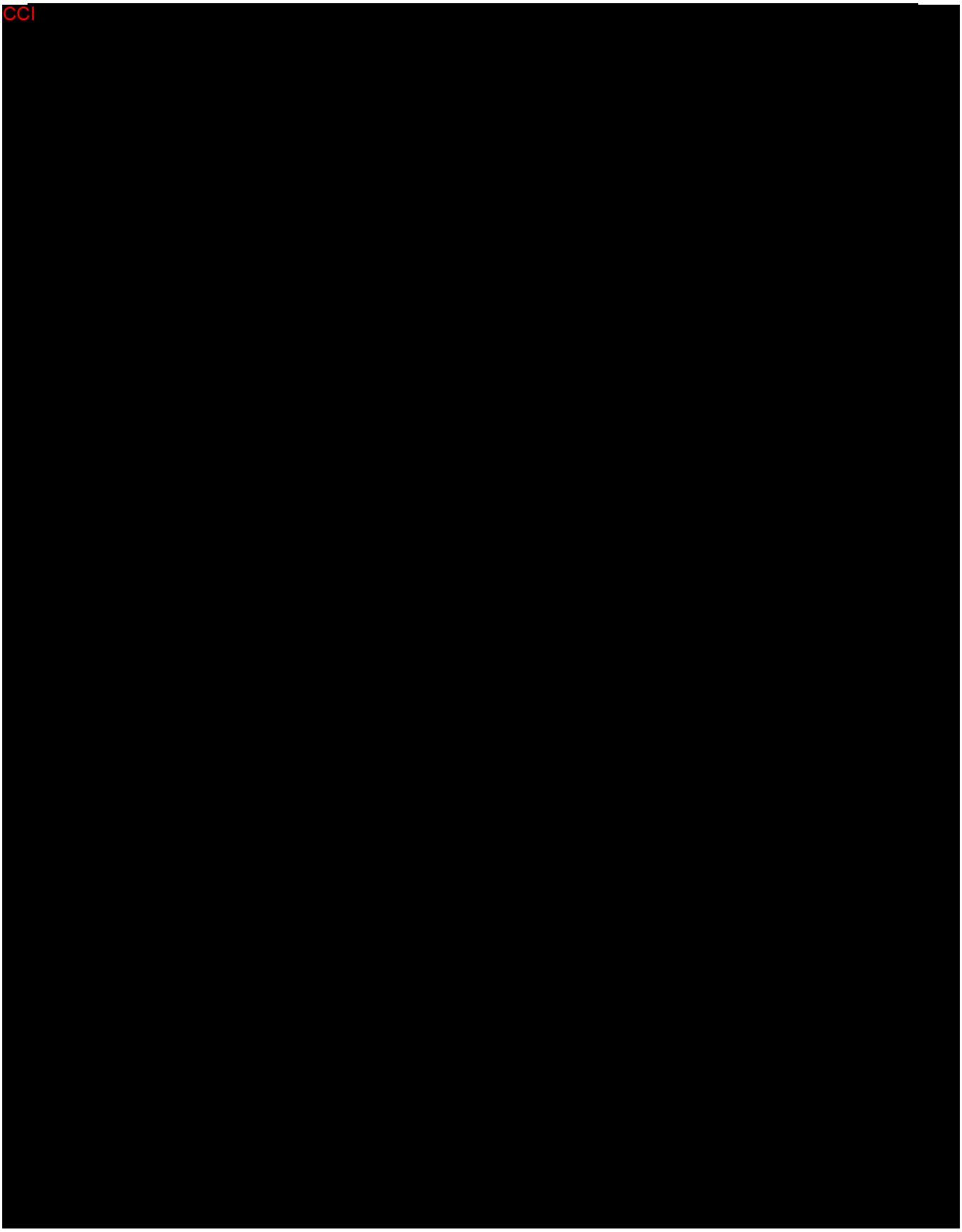


## 8.2 Randomization

Not applicable.

## 8.3 Endpoints

### 8.3.1 Primary Endpoints

The primary endpoints for the trial are:

- Phase Ia (Arm A): Occurrence of DLT up to 5 weeks after first dose of M3814 in combination with palliative fractionated RT
- Phase Ia (Arm B): Occurrence of DLT up to 12 weeks after first dose of M3814 in combination with standard CRT (with cisplatin) with curative intent
- Phase Ib (Arm A) – first 3 subjects: Occurrence of DLT up to 12 weeks after the first dose of M3814 in combination with curatively intended fractionated RT
- Phase Ib: Safety and tolerability as follows:
    - Occurrence of TEAEs (severity graded according to the NCI CTCAE v4.03)

- Results of laboratory tests, vital signs, ECGs.

### 8.3.2 Secondary Endpoints

#### 8.3.2.1 Safety Endpoints

- Occurrence of TEAEs (severity graded according to the NCI CTCAE v4.03)
- Results of laboratory tests, vital signs, ECGs.

#### 8.3.2.2 Efficacy Endpoints

- Best overall response based on tumor evaluations made by Investigator in accordance with RECIST v1.1
- Tumor size measurement based on Investigator assessment in accordance with RECIST v1.1
- PFS time defined as time from the first dose of trial treatment to progressive disease (per RECIST v1.1) based on the Investigator assessment or death from any cause, and local/local regional tumor control (Phase Ib, Arm B expansion cohort)
- OS time defined as time from the first dose of trial treatment to the date of death from any cause

#### 8.3.2.3 Pharmacokinetic Endpoints

Plasma PK parameters of M3814 for Phase Ia part (capsule):

- Fraction Day 1 – $C_{max}$, $t_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $t_{1/2}$, CL/f, Vz/f
- Fraction Day 10 – $C_{max}$, $t_{max}$, $AUC_{\tau}$, $AUC_{0-\infty}$, $t_{1/2}$, CLss/f, Vss/f, $R_{acc}$[AUC], $R_{acc}$[$C_{max}$].

Plasma PK parameters of M3814 for Phase Ia part (tablet):

- Fraction Day 1 – $C_{max}$, $t_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $t_{1/2}$, CL/f, Vz/f
- Fraction Day 6 – $C_{max}$, $t_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $t_{1/2}$, CL/f, Vz/f
- Fraction Day 10 – $C_{max}$, $t_{max}$, $AUC_{\tau}$, $AUC_{0-\infty}$, $t_{1/2}$, CLss/f, Vss/f, $R_{acc}$[AUC], $R_{acc}$[$C_{max}$].

Population PK parameters for Phase Ib and the ancillary cPoP part of the trial will be reported in a separate PK report, which will not be part of the Clinical Trial Report for this trial.

CCI [redacted]

CCI

[redacted]

## 8.4 Analysis Sets

### All Subjects Analysis Set

The All subjects (ALL) analysis set will include all the subjects who have signed the ICFs (i.e., screening failures plus subjects enrolled). The ALL analysis set will be used to summarize and describe the subject disposition, and deaths, unless otherwise stated.

### Full Analysis Set/Safety Analysis Set

The Full Analysis Set (FAS)/Safety (SAF) analysis set will include all subjects who receive at least one administration of the trial medication. The FAS/SAF analysis set will be used for all baseline, safety (except for DLTs and deaths), and efficacy summaries, unless otherwise stated.

### Dose Escalation Analysis Set

The Dose Escalation (DE) analysis set will include all subjects treated in dose escalation cohorts who receive at least 80% of M3814 and RT planned dose and complete the DLT period (through 5 weeks [Phase Ia, Arm A] or 12 weeks [Phase Ia, Arm B and Phase Ib, first 3 subjects in the expansion cohort of Arm A - NSCLC] after start of M3814 treatment). The DE set will also include subjects treated in dose escalation cohorts who experience a DLT during the DLT period regardless of the received amount of each drug. The DE analysis set will be used for the DLT summaries.

**Pharmacokinetics Analysis Set**

The PK evaluation (PK) analysis set in Phase Ia and Phase Ib parts will include subjects who have received at least the first dose of the drug and provided PK samples as per protocol for at least 6 hours following first dosing on Fraction Day 1.

CCI

[redacted]

## 8.5 Description of Statistical Analyses

### 8.5.1 General Considerations

All analyses will be prepared by formulation (capsule, tablet) and dose level (if applicable), and will be described in detail in the Statistical Analysis Plan (SAP).

The following summary statistics will be used to summarize the trial data per dose level unless otherwise specified:

- Continuous variables: number of nonmissing observations, mean, standard deviation (SD), median, minimum, and maximum, 95% CIs for the mean, as appropriate
- Categorical variables: frequencies and percentages.

The cut off for dose escalation assessments by the SMC in Phase Ia will be triggered by the completion of the DLT period of the last subject in the respective cohort.

The cut off for analysis of the secondary safety data from the Phase Ia dose escalation and MTD determination phase of the trial will be triggered when the last subject enrolled reaches the second post-treatment tumor assessment or experiences death or premature withdrawal for any reason,

whichever comes first. The cut off for the cPoP analysis will be triggered when the last subject enrolled in the ancillary cPoP part of the trial completes the assessment at the EOT visit.

The cut off for the analysis of the safety and efficacy endpoints in the Phase Ib expansion cohorts (including the first 3 NSCLC subjects treated at a lower dose) will be triggered by the date when the last enrolled subject reaches the second post-treatment tumor assessment or experiences death or premature withdrawal for any reason, whichever comes first.

Full details of the planned analyses will be described in the trial SAP separately for the dose escalation and the expansion part of the trial.

### 8.5.2 Analysis of Primary Endpoints

Phase Ia and the first 3 subjects in Phase Ib (Arm A): The number and proportion of subjects experiencing a DLT will be reported separately for each arm and formulation by dose level, based on the observation of DLTs up to 5 weeks (Phase Ia, Arm A) or 12 weeks (Phase Ia, Arm B and first 3 subjects in Phase Ib [Arm A]) after the first dose of M3814 taking into account the known toxicities with RT alone. Posterior probabilities (2.5%, 25%, 50%, 75% and 97.5% quantiles) after the last cohort will be estimated (if applicable). The DE analysis set will be used for this analysis.

### 8.5.3 Analysis of Secondary Endpoints

#### 8.5.3.1 Pharmacokinetics

##### 8.5.3.1.1 Descriptive Statistics

The PK variables will be analyzed descriptively for each treatment separately. Descriptive statistics include N, arithmetic mean, geometric mean, SD, standard error of the mean, median, minimum, maximum, coefficient of variation (%), and geometric coefficient of variation. The drug concentration in plasma at each sampling time will be presented on the original scale for all subjects who participate in the trial and provide at least 1 plasma concentration of M3814. Values below the lower limit of quantification will be taken as zero for descriptive statistics of concentrations.

Individual plasma concentration-time profiles (linear and semi-logarithmic scale) will be plotted by treatment. Mean plasma concentrations per treatment will be plotted with SD by scheduled time points. If evidence is obtained that weight affects the PK parameters, then analyses will also be performed for weight-normalized PK parameters. Formal statistical hypotheses are not set up. All statistical tests will be performed in an exploratory manner. All analyses will be based on the PK analysis set.

Details of the statistical analyses will be described in the SAP.

##### 8.5.3.1.2 Analysis of Dose Proportionality

Details of the statistical analyses will be described in the SAP.

CCI [redacted]

### 8.5.3.3 Efficacy Analyses

Summary statistics as described in Section 8.5.1 will be used for the summary of efficacy endpoints by dose level and cohort. Progression free survival and OS will be calculated for the expansion cohort only.

## 8.5.4 Analysis of Safety and Other Endpoints

### 8.5.4.1 Adverse Events

Adverse Events will be coded according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using the CTCAE (v4.03) toxicity grades. Adverse events related to trial medication will be defined as any AE considered related to M3814. In addition, missing classifications concerning trial medication relationships will be considered related to the trial drug.

The incidence and type of the following TEAEs observed until 30 days from end of treatment will be analyzed reporting separately those related to M3814, RT, CRT or their combination:

- TEAEs of any grade and SAEs
- TEAEs and SAEs of any grade related to M3814, RT, CRT or their combination
- TEAEs with CTCAE Grade ≥3
- TEAEs related to M3814, RT, CRT or their combination with CTCAE Grade ≥3
- AEs leading to withdrawal, dose modifications or permanent trial treatment discontinuation
- AEs related to M3814, RT, CRT or their combination leading to withdrawal, dose modifications or permanent trial treatment discontinuation
- AEs leading to death
- AEs related to M3814, RT, CRT or their combination leading to death.

These will be summarized according to MedDRA System Organ Classes and Preferred Terms.

Subjects who terminate treatment will be displayed in a by-subject listing, and summarized by primary withdrawal reason for each treatment group.

All reported deaths during therapy and deaths within 30 days after first and last dose of trial treatment as well as reasons for death will be tabulated (for all subjects enrolled). Deaths within 30 days from last dose administration and reasons for them will also be tabulated.

#### 8.5.4.2 Laboratory Variables

Laboratory results will be classified by grade according to the CTCAE v4.03. The worst on-trial grades after the first dose of trial treatment will be summarized.

Shifts in toxicity grades from first treatment to highest grade will be displayed. Results for variables that are not part of NCI-CTCAE (v4.03) will be presented as below, within, or above normal limits. Only subjects with post baseline laboratory values will be included in these analyses.

#### 8.5.4.3 Physical Examination

Physical examination, including vital signs (body temperature, heart rate, and blood pressure), and 12-lead ECG recorded at baseline and after administration of M3814 will be presented. Each ECG parameter will be summarized by descriptive statistics per time point, and changes from baseline will be calculated. A categorical analysis will be performed for QTcF data. Data will be further analyzed using concentration effect modeling for baseline-corrected QTcF values obtained at Day 1.

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[redacted]

## 8.6 Interim Analysis

No formal interim analyses are planned. However, administrative looks into the data may be performed.

# 9 Ethical and Regulatory Aspects

## 9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial to ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the trial.

According to United States Code of Federal Regulations Part 54.2 (e), for trials conducted in any country that could result in a product submission to the United States Food and Drug Administration for marketing approval and could contribute significantly to the demonstration of efficacy and safety of an IMP (which are considered "covered clinical trials" by the FDA), the Investigator and all subInvestigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial.

## 9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the subject about the trial and sign the ICF, as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IEC/IRB for review and opinion. Using the approved revised subject information sheet and other written information, The Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

## 9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

All subject data collected in the trial will be stored under the appropriate subject number. Only the Investigator will be able to link trial data to an individual subject via an identification list kept at the site. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but subject confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

Blood and tumor tissue samples for PGx and biomarkers will be stored for up to 12 years after trial completion. During this time, the samples may be reanalyzed for newly identified markers or with new or improved technology. After 12 years, the samples will be destroyed or fully anonymized or a new IEC/IRB approval and informed consent will be requested to keep the samples for an additional period. If tumor tissue remains, the site will be notified and the tumor tissue will be returned to the site upon request. If the site does not request the return of the tumor tissue, it will be destroyed.

## 9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the Sponsor. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial; and this may include the possibility of emergency unblinding if needed, in case of blinded trials.

Clinical trial Investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where the Investigator is not available, Merck Serono/EMD Serono provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency.

## 9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for each country participating to the trial. Insurance conditions shall meet good local standards, as applicable.

## 9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents (e.g., ICFs) to the responsible IEC or IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Trial Master File.

The IEC or IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC or IRB during the course of the trial in accordance with national regulations and requirements.

## 9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, IMP Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

# 10 Trial Management

## 10.1 Case Report Form Handling

Refer to the Manual of operations for eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection

regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. The CROs Data Management will be responsible for data processing, in accordance with the CROs standard operating procedures. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

## 10.2 Source Data and Subject Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including CT or MRI scan images, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

## 10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed

subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

## 10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

## 10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

## 10.6 Clinical Trial Report and Publication Policy

### 10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 Structure and Content of Clinical Study Reports (1996).

### 10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints and will include data from all trial sites.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission.

The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Posting of data on EudraCT and ClinicalTrials.gov is planned and will occur 12 months after the last clinic visit of the final trial subject or another appropriate date to meet applicable requirements.

# 11 References Cited in the Text

1. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361(2):123-34.

2. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434(7035):917-21.

3. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 2010;376(9737):245-51.

4. Shah BA, Qureshi MM, Logue JM, et al. Assessing cumulative acute toxicity of chemoradiotherapy in head and neck cancer with or without induction chemotherapy. Am J Otolaryngol. 2017;38(4):456-61.

5. Iqbal MS, Chaw C, Kovarik J, et al. Primary concurrent chemoradiation in head and neck cancers with weekly cisplatin chemotherapy: analysis of compliance, toxicity and survival. Int Arch Otorhinolaryngol. 2017;21(2):171-7.

6. Homma A, Inamura N, Oridate N, et al. Concomitant weekly cisplatin and radiotherapy for head and neck cancer. Jpn J Clin Oncol. 2011;41(8):980-6.

7. Noronha V, Joshi A, Patil VM, et al. Once-a-week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a Phase III randomized noninferiority trial. J Clin Oncol. 2018;36(11):1064-72.

8. Das S, Thomas S, Pal SK, et al. Hypofractionated palliative radiotherapy in locally advanced inoperable head and neck cancer: CMC Vellore experience. Indian J Palliat Care. 2013;19(2):93-8.

9. Mosteller RD. Simplified Calculation of Body Surface Area. N Engl J Med 1987;317(17):1098.

10. Drug Development and Drug Interactions. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm Accessed on 14 May 2015.

[redacted]

# 12 Appendices

## Appendix A: Signature Pages and Responsible Persons for the Trial



Document No. CCI
Object No. CCI
Global Version ID: CCI

## Signature Page – Protocol Lead

| | |
|---|---|
| **Trial Title:** | An Open Label, Phase Ia/Ib Trial of the DNA-PK Inhibitor MSC2490484A in Combination with Radiotherapy in Patients with Advanced Solid Tumors |
| **IND Number:** | CCI |
| **EudraCT Number:** | 2015-000673-12 |
| **Clinical Trial Protocol Date / Version:** | 31 January 2019/Version 9.0 |

**Protocol Lead responsible for designing the clinical trial:**

I approve the design of the clinical trial:

PPD

Signature

PPD

Date of Signature

| | |
|---|---|
| **Name, academic degree:** | PPD |
| **Function / Title:** | |
| **Institution:** | Merck KGaA |
| **Address:** | Frankfurter Strasse 250, 64293 Darmstadt, Germany |
| **Telephone number:** | PPD |
| **Fax number:** | Not applicable |
| **E-mail address:** | PPD |

## Signature Page – Coordinating Investigator

| | |
|---|---|
| **Trial Title** | An Open Label, Phase Ia/Ib Trial of the DNA-PK Inhibitor MSC2490484A in Combination with Radiotherapy in Patients with Advanced Solid Tumors |
| **IND Number:** | CCI [redacted] |
| **EudraCT Number** | 2015-000673-12 |
| **Clinical Trial Protocol Date / Version** | 31 January 2019/Version 9.0 |

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD [redacted]

Signature

PPD [redacted]

Date of Signature

| | |
|---|---|
| **Name, academic degree:** | PPD [redacted] |
| **Function / Title:** | |
| **Institution:** | |
| **Address:** | |
| **Telephone number:** | |
| **E-mail address** | |

## Signature Page – Principal Investigator

| | |
|---|---|
| **Trial Title** | An Open Label, Phase Ia/Ib Trial of the DNA-PK Inhibitor MSC2490484A in Combination with Radiotherapy in Patients with Advanced Solid Tumors |
| **IND Number:** | CCI [redacted] |
| **EudraCT Number** | 2015-000673-12 |
| **Clinical Trial Protocol Date / Version** | 31 January 2019/Version 9.0 |
| **Center Number** | |
| **Principal Investigator** | |

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical trials to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

**Name, academic degree:**

**Function / Title:**

**Institution:**

**Address:**

**Telephone number:**

**Fax number:**

**E-mail address:**

## Sponsor Responsible Persons not Named on the Cover Page

| | |
|---|---|
| Name | PPD |
| Function | Biostatistician |
| Institution | Merck KGaA |
| Address | Frankfurter Strasse 250, 64293 Darmstadt, Germany |
| Telephone number | PPD |
| E-mail address | PPD |

| | |
|---|---|
| Name | PPD |
| Function | Principal Clinical Trial Lead |
| Institution | Merck KGaA |
| Address | Frankfurter Strasse 250, 64293 Darmstadt, Germany |
| Telephone number | PPD |
| E-mail address | PPD |

# Appendix B: Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

For details, please refer to the following paper by Eisenhauer et al.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

***Definitions***

At Baseline (within 4 weeks of initiation of treatment), tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

**Measurable:**

- *Tumor lesions*: Must 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 which cannot be accurately measured with calipers should be recorded as non-measurable),
  - 20 mm by chest X-ray.
- *Malignant lymph nodes*: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At Baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and nontarget lesions" for information on lymph node measurement.

**Non-measurable**

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

**Special considerations regarding lesion measurability**

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

*Bone lesions:*

- Bone scan, positron emission tomography scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of 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, MRI, or other established methods can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

*Cystic lesions:*

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) 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 measurability described above. However, if noncystic 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 other locoregional therapy area are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

***Methods of measurement***

- 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.

- Method of assessment

  The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

  - *Chest X-ray*: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since 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 is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. An MRI is also acceptable in certain situations (e.g., for body scans).
- *Ultrasound*: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
- *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 CR or surgical resection is an endpoint.
- *Tumor markers*: Tumor markers alone cannot be used to assess objective tumor response.
- *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.

***Tumor response evaluation***

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at Baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at Baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. Response criteria are listed in Table E.1 and Table E.2.

**Response Criteria**

**Table E.1**

| **Evaluation of target lesions** | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) 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 reference the baseline sum diameters. |
| Progressive Disease | At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). |
| Stable Disease | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on trial |

**Table E.2**

| Evaluation of nontarget lesions | |
|---|---|
| Complete Response (CR) | Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis). |
| Stable Disease | Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits. |
| Progressive Disease | Unequivocal progression (see comments below) of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression). |

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

### Evaluation of best overall response

It is assumed that at each protocol specified time point, a response assessment occurs. Table E-3 below provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

**Table E-3**

| Target lesions | Nontarget lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-progressive disease | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non- progressive disease or not all evaluated | No | PR |
| Stable disease | Non- progressive disease or not all evaluated | No | Stable disease |
| Not all evaluated | Non progressive disease | No | NE |
| Progressive disease | Any | Yes or No | Progressive disease |
| Any | Progressive disease | Yes or No | Progressive disease |
| Any | Any | Yes | Progressive disease |

Abbreviations: CR=complete response, NE=not evaluable; PR=partial response.

The best overall response is determined once all the data for the subject is known.

Best response determination in trials where confirmation of CR or PR IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has stable disease at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When stable disease is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when stable disease is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has stable disease at first assessment, progressive disease at second and does not meet minimum duration for stable disease, will have a best response of progressive disease. The same subject lost to follow-up after the first stable disease assessment would be considered not evaluable.

Best response determination in trials where confirmation of CR or PR IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (at least 4 weeks apart). In this circumstance, the best overall response can be interpreted as in Table E-4.

**Table E-4**

| Overall response | Overall response | BEST overall response |
|---|---|---|
| **First time point** | **Subsequent time point** | |
| CR | CR | CR |
| CR | PR | Stable disease, progressive disease, or PR[a] |
| CR | Stable disease | Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease |
| CR | Progressive disease | Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease |
| CR | NE | Stable disease provided minimum criteria for stable disease duration met, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | Stable disease | Stable disease |
| PR | Progressive disease | Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease |
| PR | NE | Stable disease provided minimum criteria for stable disease duration met, otherwise NE |
| NE | NE | NE |

Abbreviations: CR=complete response, NE=not evaluable, PR=partial response,

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease progressive disease at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for stable disease was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

PPD

PPD

# Appendix D: Outline of Intensity-modulated Radiotherapy

In the planning of RT, intensity modulated RT (IMRT) must be used. The dose planning can be CT or positron emission tomography-CT (PET-CT) according to institutional guidelines.

The use of daily image guided RT (IGRT) is recommended.

For patients with SCCHN, the total dose of RT is 66 to 70 Gy given in 33 to 35 fractions and for patients with NSCLC, the total dose of RT is 66 Gy given in 33 fractions. Simultaneous integrated or sequential boost should be given according to institutional guidelines.

**Organs at risk to be contoured**

SCCHN:

| | |
|---|---|
| Parotid gland | Required |
| Spinal cord | Required |
| Optic chiasm | Required |
| Brain stem | Required |
| Oral cavity | Facultative |
| Brachial plexus | Facultative |
| Mandible | Facultative |
| Pharyngeal constrictor muscle | Facultative |
| Cochlea | Facultative |
| Esophagus | Facultative |
| Lungs | Facultative |
| External border of patients | Facultative |

NSCLC:

| | |
|---|---|
| Spinal cord | Required |
| Brachial plexus | Facultative |
| Heart | Required |
| Coronary arteries | Required |
| Stomach, liver and kidney (if included in field) | Required |
| Esophagus | Required |
| Lungs | Required |
| External border of patients | Required |

# Appendix E: Contraceptive Guidance and Women of Childbearing Potential

## Definitions

### Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

### Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
2. Premenarchal
3. Postmenopausal female
   - Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

## Contraceptive Guidance

| Highly Effective Contraceptive Methods That Are User Dependent<br>Failure rate of <1% per year when used consistently and correctly. |
|---|
| • Combined (estrogen- and progestogen-containing ) hormonal contraception associated with inhibition of ovulation[b]<br>  • oral<br>  • intravaginal<br>  • transdermal |
| • Progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>  • oral<br>  • injectable |

| Highly Effective Methods That Are User Independent |
|---|
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>• Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (IUS)<br>• bilateral tubal occlusion |
| • Vasectomized partner<br>(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.) |
| • Sexual abstinence<br>(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant.) |
| NOTES:<br>a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with ocal regulations regarding the use of contraceptive methods for participants participating in clinical studies.<br>b) Hormonal contraception may be susceptible to interaction with the trial drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 90 days after the last dose of trial treatment. |