### 16.1.9. Documentation of statistical methods

Hardware and software tools

Statistical analysis plan Version 2.0 dated 11 July 2023

Statistical analyses were performed using SAS®/PC Software version 9.2.

Coding was performed using Medical Dictionary for Regulatory Activities for the medical events and World Health Drug Dictionary for the treatments.

I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

| | |
|---|---|
| *Document title* | **STATISTICAL ANALYSIS PLAN (SAP)** |
| *Study official title* | **A randomised, open-label, multi-centre, two-arm Phase 3 study comparing futuximab/modotuximab in combination with trifluridine/tipiracil to trifluridine/tipiracil single agent with a Safety Lead-In part in participants with KRAS/NRAS and BRAF wild type metastatic colorectal cancer previously treated with standard treatment and anti-EGFR therapy** |
| *Study brief title* | **Phase 3 study of futuximab/modotuximab in combination with trifluridine/tipiracil *versus* trifluridine/tipiracil single agent in participants with previously treated metastatic colorectal cancer** |
| *Test drug code* | **Futuximab/modotuximab (also known as S95026 or Sym004)** |
| *Indication(s)* | **Pre-treated metastatic colorectal cancer** |
| *Development phase* | **Phase 3 with Safety Lead-In Part** |
| *Protocol code* | **CL3-95026-001** |
| *EudraCT Number* | **2021-003151-41** |
| *Universal Trial Number* | **Not applicable** |
| *Sponsor* | **Institut de Recherches Internationales Servier (I.R.I.S.)** |
| *Date of the document* | **11 July 2023** |
| *Version of the document* | **Version 2.0** |
| *Author(s) of the document* | PPD **(Biostatistician – IVIDATA LIFE SCIENCES)**<br>PPD **(Biostatistician – I.R.I.S.)** |

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CCI

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

Signature Page for VV-TMF-130355 v1.0

Reason for signing: Approved

Name: PPD
Role: CTI
Date of signature: 13-Jul-2023 07:59:26 GMT+0000

Reason for signing: Approved

Name: PPD
Role: Biostatistics - CentEX MVD
Date of signature: 18-Jul-2023 10:29:58 GMT+0000

Signature Page for VV-TMF-130355 v1.0

**Follow up of versions**

| Version | Release date (dd/mm/yyyy) | Key modifications(*) | Impact |
|---|---|---|---|
| V1.0 | 04/02/2022 | Not applicable. | |
| V2.0 | 15/03/2023 | As the Randomized part has been cancelled due to study discontinuation during the Safety Lead-In part, all the methods and analyses related to Randomized part have been removed.<br>- In addition:Section 3.2.4: deletion of some descriptive tables of baseline characteristics<br>- Section 3.3: deletion by class analyses<br>- Section 3.4: deletion of efficacy analyses, except the BOR analysis<br>- Section 3.5.1: addition of related TEAE leading to death description<br>- Section 3.5.2: deletion of descriptive tables for deaths<br>- Section 3.5.3: descriptive tables by visit restricted to cycle 1 and addition of shift tables for baseline vs last values under treatment<br>- Section 3.5.4: descriptive tables by visit restricted to last value<br>- Section 3.5.5: descriptive tables by visit restricted to last value<br>- Section 5.1: update of the first and last IMP intakes definitions<br>- Section 7.3 update Table - Gradable and non-gradable laboratory parameters | |
| | | | |

*(*) Main changes as compared to the statistical analyses planned in the protocol for the first SAP signed version (1.0). Main changes from the previous signed version for the other SAP signed version(s).*

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

**Table of contents**

**List of tables**

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

**List of figures**

**List of abbreviations**

| | | |
|---|---|---|
| ADA | : | Anti-drug Antibody |
| AE | : | Adverse Event |
| ALT | : | ALanine (Amino)Transferase |
| ALP | : | ALkaline Phosphatase |
| ANCOVA | : | Analysis of Covariance |
| AST | : | ASpartate (Amino)Transferase |
| AUC | : | Area Under the Plasma Concentration-Time Curve |
| BID | : | Twice Daily |
| BOR | : | Best Overall Response |
| BPM | : | Beats per Minute |
| BSA | : | Body Surface Area |
| CI | : | Confidence Interval |
| CLcr | : | Creatinine clearance |
| cm | : | Centimetre |
| CMH | : | Cochran-Mantel-Haenszel |
| CR | : | Complete Response |
| CRF | : | Case Report Form |
| CTCAE | : | Common Terminology Criteria for Adverse Events |
| ctDNA | : | Circulating tumour DNA |
| DAP | : | Data Analysis Plan |
| DBP | : | Diastolic Blood Pressure |
| DCR | : | Disease Control Rate |
| DI | : | Dose Intensity |
| DLT | : | Dose-Limiting Toxicity |
| DMC | : | Data Monitoring Committee |
| DN | : | Double-Negative |
| DoR | : | Duration of Response |
| ECD | : | Extracellular Domain |
| ECG | : | ElectroCardioGram |
| ECOG PS | : | Eastern Cooperative Oncology Group Performance Status |
| e-CRF | : | Electronic Case Report Form |
| EGFR | : | Epidermal Growth Factor Receptor |
| EORTC | : | European Organisation for Research and Treatment of Cancer |

| | | |
|---|---|---|
| FAS | : | Full Analysis Set |
| GCP | : | Good Clinical Practice |
| GGT | : | Gamma-Glutamyl Transferase (Gamma-Glutamyl Transpeptidase) |
| GHS | : | Global Health Status |
| HR | : | Heart Rate |
| HR | : | Hazard Ratio |
| ICF | : | Informed Consent Form |
| ICH | : | International Conference on Harmonization |
| IE | : | Intercurrent Event |
| IMP | : | Investigational Medicinal Product |
| INR | : | International Normalized Ratio |
| I.R.I.S. | : | Institut de Recherches Internationales Servier |
| ITT | : | Intention-To-Treat |
| IU | : | International Unit |
| IV | : | IntraVenous (route) |
| IWRS | : | Interactive Web Response System |
| KRAS | : | V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog |
| LDH | : | Lactate DeHydrogenase |
| LLN | : | Lower Limit of Normal laboratory reference range |
| MedDRA | : | Medical Dictionary for Regulatory Activities |
| MMRM | : | Mixed-effects Model Repeated Measures |
| NCI | : | National Cancer Institute |
| NCI-CTCAE | : | National Cancer Institute - Common Terminology Criteria For Adverse Events |
| NLR | : | Neutrophils lymphocytes ratio |
| OR | : | Objective Response |
| ORR | : | Overall Response Rate |
| OS | : | Overall Survival |
| PD | : | Progressive Disease |
| PD | : | Pharmacodynamics |
| PFS | : | Progression Free Survival |
| PK | : | Pharmacokinetics |
| PR | : | Partial Response |
| PRO | : | Patient Reported Outcome |
| PS | : | Performance Status |

| | | |
|---|---|---|
| PT | : | Preferred Term |
| PV | : | PharmacoVigilance |
| QLQ | : | Quality of Life Questionary |
| QoL | : | Quality of Life |
| QTc | : | QT interval corrected for heart rate |
| QTcB | : | Bazett's corrected QT interval |
| QTcF | : | Fridericia's corrected QT interval |
| RDI | : | Relative Dose Intensity |
| RECIST | : | Response Evaluation Criteria In Solid Tumours |
| RMST | : | Restricted mean survival time |
| SAE | : | Serious Adverse Event |
| SAP | : | Statistical Analysis Plan |
| SBP | : | Systolic Blood Pressure |
| SD | : | Standard Deviation |
| SD | : | Stable Disease |
| SOC | : | System Organ Class |
| SS | : | Safety Set |
| TEAE | : | Treatment Emergent Adverse Event |
| STEAE | : | Serious Treatment Emergent Adverse Event |
| TLG | : | Tables, Listings and Graphs |
| TN | : | Triple Negative |
| TR | : | Tumour Response |
| TtPS2 | : | Time to ECOG Performance Status ≥ 2 |
| TTNT | : | Time to Next Treatment |
| TTR | : | Time to Response |
| TUDD | : | Time until definitive deterioration |
| ULN | : | Upper Limit of Normal laboratory reference range |
| VAS | : | Visual Analogue Scale |
| VEGF | : | Vascular Endothelial Growth Factor |
| WBC | : | White Blood Cells |
| WHO | : | World Health Organization |
| WT | : | Wild Type |
| WV | : | Withdrawal Visit |

# 1. INTRODUCTION

This Statistical Analysis Plan (SAP) details the planned analyses to be performed for the Safety Lead-In part, in accordance with the main characteristics of the amended clinical study protocol of 16th August 2022.

The randomised part has been cancelled due to study discontinuation during the Safety Lead-in part for strategic reasons. All information concerning the randomised part is described in the protocol.

The templates for Tables, Listings and Graphs (TLG) are described in a separate document.

## 1.1. Study objectives

**Safety Lead-In part**

**Primary**

- To assess safety and tolerability of futuximab/modotuximab in combination with trifluridine/tipiracil according to National Cancer Institute Comment Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

**Secondary**

- To assess anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil per investigator assessment using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 in terms of:
  - Objective Response Rate (ORR).
  - Best Overall Response (BOR).
  - Disease Control Rate (DCR).
  - Progression Free Survival (PFS).
- To assess anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil in terms of:
  - Overall Survival (OS).
- To characterise the pharmacokinetic (PK) profile of futuximab/modotuximab, trifluridine and tipiracil in the combination of futuximab/modotuximab with trifluridine/tipiracil.
  To evaluate the immunogenicity of futuximab/modotuximab (*i.e.* occurrence of anti-drug antibody [ADA]).

**Exploratory**

- To explore biomarkers as potential predictors of response and to track the emergence of resistance.

Thereafter, only the primary analysis and the BOR of the secondary analysis will be assessed.

## 1.2. Study design

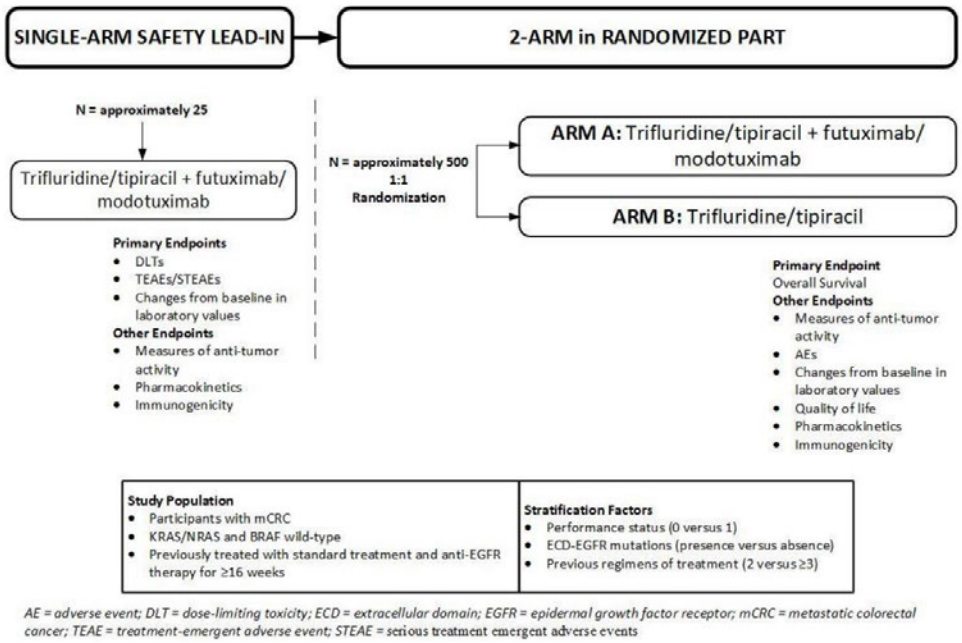
### 1.2.1. Study plan

This is a randomised, open label, multi-centre, two-arm Phase 3 study to evaluate futuximab/modotuximab in combination with trifluridine/tipiracil *versus* trifluridine/tipiracil monotherapy in participants ≥ 18 years of age with KRAS/NRAS and BRAF WT mCRC who were previously treated by chemotherapy (including oxaliplatin, irinotecan and 5-fluorouracil, anti-VEGF agents) and with anti-EGFR mAb therapy for ≥ 16 weeks.

Initially, the study comprises two parts a Safety Lead-In part in approximately 25 participants.

The initial study design is depicted in Figure (1.2.1) 1, Figure (1.2.1) 2 and Figure (1.2.1) 3.

**Figure (1.2.1) 1 - CL3-95026-001 Study Design**




*AE = adverse event; DLT = dose-limiting toxicity; ECD = extracellular domain; EGFR = epidermal growth factor receptor; mCRC = metastatic colorectal cancer; TEAE = treatment-emergent adverse event; STEAE = serious treatment emergent adverse events*

**Figure (1.2.1) 2 - Study plan for the Safety Lead-In Part**

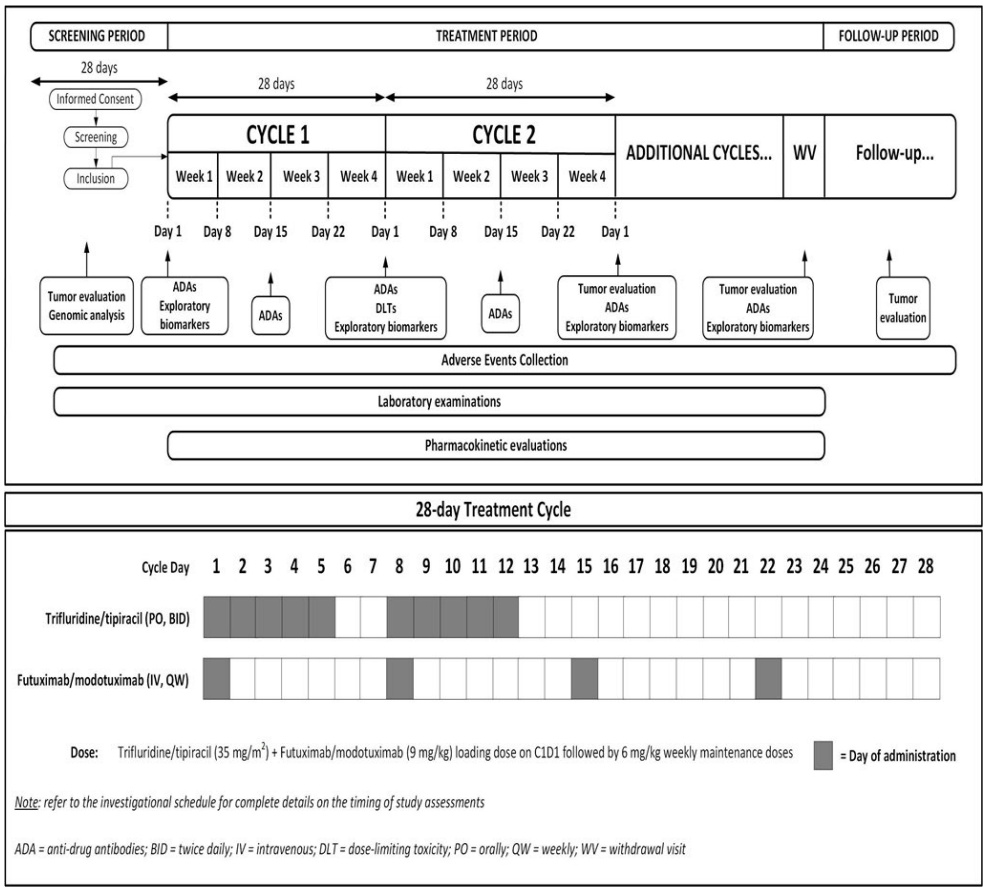
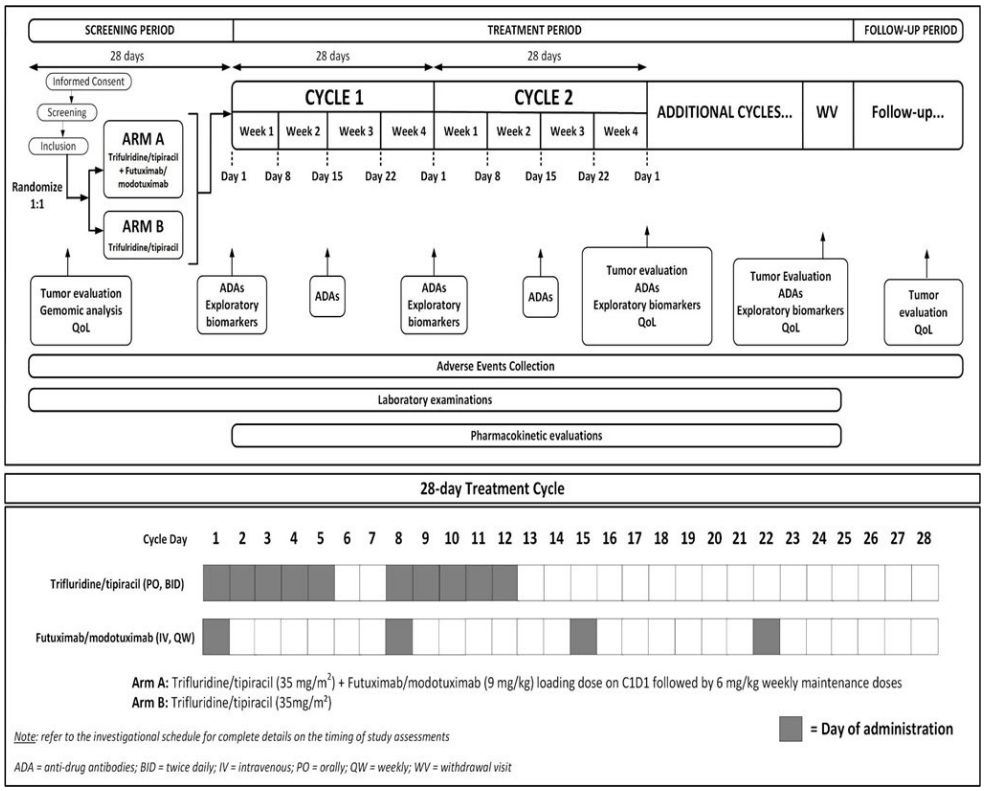


**Figure (1.2.1) 3 - Study plan for the randomised Part**




The study start is defined as the date of the first visit of the first participant.

The study will be divided into the following periods for each participant:

- Screening visit/Screening period (maximum 28 days):
  - Screening visit: after signature of the Informed Consent Form(s) (ICF) to check screening criteria and decide if participant can be screened for the study.
  - Screening period: if the participant is screened in the study, check the inclusion and exclusion criteria and decide if participant can be included in the study.
- Treatment period: participants will be treated until they meet a discontinuation criterion as described in Section 5.8.1 of the protocol. The participants should receive the first dose of first IMP (Day 1 of Cycle 1) within 3 days after inclusion.
- Withdrawal visit (WV): should be conducted within approximately 4 weeks following the date of study treatment withdrawal and before the start of a new anticancer therapy.

- Follow-up period: after the WV the participant will be followed every 8 weeks (± 10 calendar days):
  - For survival status until the end of the study. This follow-up can be done remotely by using various telecommunication technologies including but not limited to phone, internet and shared electronic medical records.
  - For tumour assessment (if the patient was withdrawn from the study for another reason than radiologic disease progression) (compared to the last assessment) until radiologic progression regardless of initiation of new anticancer therapy.

End of Trial is defined as the date of the last follow-up of the last participant (including a contact phone), or the date of last contact attempt if the last participant is declared lost to follow-up, or when the target number of OS events is reached, whichever occurs first.

Any participants still receiving IMPs at the end of the study will be allowed to continue at the discretion of the investigator and as long as none of the treatment discontinuation criteria are met.

If some participants are still receiving study treatments when the end of study is met, please see Section 6.5 of the protocol for procedures to be followed.

Due to the exceptional circumstances in relation to the coronavirus disease pandemic, the sponsor, in accordance with competent regulatory authority's guidelines, could decide to implement precautionary measures during the study to ensure participants safety, while maintaining compliance with GCP and study data integrity. These precautionary measures will remain in effect only for the duration of national public health emergency.

### 1.2.2. Randomisation

Not applicable due to the cancellation of the randomised part.

## 1.3. Determination of sample size

Approximately 25 participants will be evaluated in Safety Lead-In part. The DMC will initially determine tolerability after 6 evaluable participants have been treated. If ≤ 2 participants out of the first 6 evaluable participants experience a DLT, and the DMC based on the totality of safety data determines the doses to be tolerable, then the Safety Lead-In will be expanded by an additional cohort of 6 participants. The DMC will again assess the tolerability when 12 participants have been enrolled and the 12th participant has completed the first treatment cycle. If ≤ 3 participants experience a DLT, and the DMC based on the totality of safety data determines the doses to betolerable, the Safety Lead-In will be expanded to add another 13 participants, for a total of25 participants. The DMC will meet again at the end of the Safety Lead-In part when approximately 25 participants have been treated.

## 2. ANALYSIS SETS AND SUBGROUPS / TREATMENT GROUPS

### 2.1. Analysis sets

Screened set**:** All patients screened.

Safety Set (SS): All participants having taken at least one dose of IMPs.. SS will be used in all analyses.

DLT Evaluable Set (DLTES): all participants in the SS who are evaluable for DLT. DLTES will be used in safety analyses, when specified.

### 2.2. Treatment groups

Treatment considered for the analysis will be the following:
- Futuximab/modotuximab + trifluridine/tipiracil

### 2.3. Subgroups

Not applicable.

## 3. STATISTICAL METHODS

### 3.1. General considerations

The following descriptive statistics will be provided depending on the nature of considered data:

**Qualitative data:** number of observed values, number and percentage of patients per class.

**Quantitative data:** number of observed values, mean and standard deviation, median, first and third quartiles, minimum and maximum.

Descriptive summary statistics (n, mean (SD), median, min and max) will be provided for variables measured on a continuous scale.

The frequency distribution (n, %) will be provided for variables measured on a nominal scale.

### 3.2. Disposition and baseline characteristics

The participants' disposition and baseline characteristics will be described in SS.

The number of participants in each study population and the reasons for exclusion will be summarized as well as the disposition of participants, including reasons for discontinuation and protocol deviations at baseline and during study.

Characteristics of participants including demography, characteristics of the disease at diagnosis and study entry, medical history, prior therapy and concomitant medication at baseline will be summarized.

### 3.2.1. Disposition of patients

Disposition of patients will be described in the Screened Set before and at inclusion and in the SS after the inclusion.

### 3.2.2. Protocol deviations

All important protocol deviations before or at inclusion, as well as after inclusion, will be described in the SS, by category of deviations based on ICH E3 guideline and ICH E3 Q&A.

### 3.2.3. Study population

The number of patients in each study population and the reasons for exclusion will be summarized.

### 3.2.4. Demographic data and other baseline characteristics

#### 3.2.4.1. Demographic characteristics

The following demographic and baseline variables will be summarized for patients in the SS:

- Age (years).
-
- Gender (Female, Male).
- Race (White, American Indian or Alaska native, Asian, Black or African American, Native Hawaiian/Other Pacific Islander, Other).
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino).
-
- Country.
- Pregnancy test.

#### 3.2.4.2. History of cancer

Nature and duration of cancer will be summarized in the SS according to the following variables:

- Primary diagnosis (Adenocarcinoma of colorectal cancer, Other).
- Primary tumour site (Cecum, Appendix, Ascending colon, Hepatic flexure, Splenic flexure, Descending colon, Sigmoid colon, Rectosigmoid segment, Right colon, Left colon, Rectum, Transverse colon, Multilocalised right colon, Multilocalised left colon, Other).
- Primary tumour localisation (Right, Left) (5 Appendix A).
- Current tumour status: metastasis (Yes, No).
- Site of metastasis (regional lymph node, distant lymph node, lung, liver, bone, brain, skin, peritoneal, soft tissue, other).
- Number of metastatic sites.
- Disease duration (years).
- Time from first metastasis diagnosis to inclusion (months).
- Progression free interval (months).
- Treatment free interval (months).

A listing of the history of colorectal cancer will also be provided. It will include the following information: Disease duration (years), time from first metastasis diagnosis to inclusion (months), primary diagnosis, primary tumour site, metastatic sites, progression free interval (months) and treatment free interval (months).

#### 3.2.4.3. Signs and symptoms related to colorectal cancer

Not applicable.

#### 3.2.4.4. Medical and surgical history not related to colorectal cancer

Not applicable.

#### 3.2.4.5. Previous therapies related to colorectal cancer

All previous therapies for the colorectal cancer will be summarized according to the following variables for patients in the SS:

- Previous neo-adjuvant drug treatment (Yes, No).
- Previous adjuvant drug treatment (Yes, No).
- Previous adjuvant and neo-adjuvant drug treatment (Yes, No).
- Previous adjuvant or neo-adjuvant drug treatment (Yes, No).
- Previous metastatic drug treatment (Yes, No).
- Previous adjuvant or neo-adjuvant fluoropyrimidine (Yes, No).
- Previous metastatic fluoropyrimidine (Yes, No).
- Previous metastatic irinotecan (Yes, No).
- Previous adjuvant or neo-adjuvant oxaliplatin (Yes, No).
- Previous metastatic oxaliplatin (Yes, No).
- Previous metastatic anti-VEGF monoclonal Anti Body (Yes, No).
- Previous neo-adjuvant anti-EGFR monoclonal Anti Body (Yes, No) in RAS wild type patients only as documented in the e-CRF.
- Previous metastatic anti-EGFR monoclonal Anti Body (Yes, No).
- Response to previous metastatic regimen containing anti-EGFR monoclonal Anti Body (CR, PR, SD).
- Skin toxicity with previous metastatic regimen containing anti-EGFR monoclonal Anti Body (Yes, No).
- Skin toxicity with previous metastatic regimen containing anti-EGFR monoclonal Anti Body (Grade 1-2, Grade 3-4, No skin toxicity).
- Duration of previous metastatic regimen containing anti-EGFR monoclonal Anti Body.
- Number of prior regimens for mCRC.
- Number of prior adjuvant or neoadjuvant regimens.
- Reason for treatment discontinuation of the last regimen prior to randomisation (Toxicity, Progressive disease, Other).
- Last regimen prior to randomisation containing anti-EGFR monoclonal Anti Body (Yes, No).

#### 3.2.4.6. Vital signs and clinical examination at baseline

Refers to section 3.5.4..

#### 3.2.4.7. ECG at baseline

Refers to section 3.5.5.

#### 3.2.4.8. Clinical laboratory at baseline

All laboratory data will be analysed using NCI-CTCAE grade criteria.
Clinical laboratory parameters will be summarized in the SS according to the following classes:

- For highest and/or lowest gradable parameters at baseline: (Grade 0, Grade 1, Grade 2, Grade 3, Grade 4).
- For non-gradable parameters and gradable parameters without baseline, except for creatinine clearance: (< LLN, [LLN, ULN], > ULN).
- For urinalysis parameters, except for specific gravity and pH: (Absence, Trace, Presence (+, More than one +)).

Creatinine clearance will be categorised in 4 levels of impairment and analysed by classes (severe, moderate, mild, normal):

- Normal renal function (CLcr ≥ 90 mL/min).
- Mild renal impairment (CLcr 60-89 mL/min).
- Moderate renal impairment (CLcr 30-59 mL/min).
- Severe (CLcr < 30 mL/min).

### 3.3. Treatments

#### 3.3.1. Extent of exposure and treatment compliance

#### 3.3.1.1. Trifluridine/tipiracil

Extent of exposure and treatment compliance of trifluridine/tipiracil will be described in the SS by patient overall including:

- Treatment duration (months).
- Follow-up duration (months) with median based on reverse Kaplan Meier method.
- Number of cycles per patient.
- Cumulative dose (mg/m$^2$).
- Dose intensity (DI) (mg/m$^2$/week).
- Relative Dose Intensity (RDI) (%).
- Patients with at least one dose reduction (Yes, No).
- Number of dose reductions per patient.
- Number of patients by actual dose level on day 1 of each cycle.
- Patients with at least one dispensation postponed (Yes, No).
- Number of dispensations postponed per patient.
- Patients with at least one unplanned treatment interruption (Yes, No).
- Number of unplanned treatment interruptions per patient.

Individual listings by cycle will be provided including: cumulative dose, planned dose intensity, DI, RDI, total number of tablets given, estimated and returned (15 or 20 mg for trifluridine/tipiracil), cycle duration (weeks), duration of unplanned treatment interruption (days), reason for interruption, dispensation postponed (Yes, No), reason for dispensation postponed (medical reason, non-medical reason) and dose reduction (Yes, No).

Individual listing per patient will be provided including: number of cycles, cumulative dose, planned dose intensity, DI, RDI, treatment duration, unplanned treatment interruption (days), number of dispensations postponed and number of dose reductions.

#### 3.3.1.2. Futuximab/modotuximab

Number of infusions per patient, patients with full dose administered, patients with at least one missed infusion, number of cycles with at least one missed infusion, patients with infusion interrupted, patients with infusion rate decreased, cumulative dose (mg/kg), DI (mg/kg/week) and RDI (%)will be described by patient in the SS.

Individual listing by cycle will be provided including: number of infusions, reason for missed infusion (medical reason, non-medical reason), cumulative dose, planned dose intensity, DI, RDI, cycle duration (weeks), full dose administered (Yes, No), reason for incomplete volume infusion (medical reason, non-medical reason), infusion postponed (Yes, No), reason for postponed infusion (medical reason, non-medical reason), reason for infusion interrupted (medical reason, non-medical reason) and infusion rate decreased (Yes, No).

Individual listing per patient will be provided including: number of cycles, number of infusions, cumulative dose, planned dose intensity, DI, RDI, treatment duration (months), number of cycles with at least one partial dose administered, number of cycles with infusion postponed, number of cycles with infusion interrupted and number of cycles with infusion rate decreased.

### 3.3.2. Concomitant treatments and new anti-cancer therapies

Drug treatments will be described by pharmacological class, pharmacological sub-class, therapeutic class and preferred name (WHO-DD classification, latest available version at the analysis date). All concomitant treatments and new anti-cancer therapies will be summarized according to the following variables:

- Concomitant treatment (Yes, No).
- Received new drug treatment (Yes, No).

Concomitant treatments taken at inclusion, those taken before, during and after the treatment period, as well as new anticancer therapies will be described in the SS.

For concomitant treatments as well as new drug treatments, individual listing will be provided including pharmacological class, pharmacological sub-class, therapeutic class and preferred name, medications start and end date, administration schedule and dose unit administered. The listing will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

## 3.4. Efficacy analysis

The proportion of participants with BOR according to RECIST version 1.1 criteria and using investigator's tumour assessment will be summarized descriptively.

A waterfall plot displaying the best relative change of the sum of the lesions diameters from baseline will be performed.

### 3.5. Safety analysis

All safety analyses will be performed in the SS unless otherwise specified.

Calculation rules for safety endpoints and other specific definitions are provided in 7 Appendix C.

Adverse events (AEs) will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events CTCAE version 5.0.

#### 3.5.1. Adverse events

Treatment-emergent adverse events (TEAE) are defined as any AEs reported from the date of first administration of IMP to 30 days after the last date of IMP administration.

Number of events, number and percentage of patients reporting at least one event, presented by SOC and/or PT (depending on the analysis) will be provided for serious adverse events (SAE) and TEAE over the study and treatment periods, respectively.

TEAE and Serious TEAE (STEAE) will be described according to:
- Worst grade.
- Severity.
- Relationship (related to trifluridine/tipiracil, related to Futuximab/modotuximab, related to the combination) (8 Appendix D).
- Outcome (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, unknown).
- Leading to drug withdrawal (leading to trifluridine/tipiracil withdrawal, leading to Futuximab/modotuximab withdrawal).

TEAE will be also described according to:
- Action taken regarding IMPs (drug interrupted, dose reduced, dose delayed, dose reduced or delayed, dose reduced and delayed, dose not changed, infusion rate reduced).
- TEAE related to disease progression.
- TEAE leading to death.
- TEAE related (related to trifluridine/tipiracil, related to Futuximab/modotuximab, related to the combination) leading to death
- Requirement of added therapy.

Non-STEAE (EudraCT analyses) and Non-STEAE related to IMPs will be described by SOC and PT.

Number and percentage of participants who experienced a DLT will be summarized and listed in the DLTES.

#### 3.5.2. Death

Listing of patients who died during the treatment period or during the follow-up period will be provided.

### 3.5.3. Clinical laboratory evaluation

For haematological, biochemistry, coagulation and urinary parameters, descriptive statistics on value at baseline and on worst value at cycle 1 will be provided.

Number and percentage of patients for each laboratory parameter classified according to: reference ranges (< LLN/≥ LLN or ≤ ULN/> ULN) for non-gradable parameters except creatinine clearance, grade (Grade 0, Grade 1, Grade 2, Grade 3, Grade 4) for gradable parameters, following classes for proteinuria (Absence, Trace, Presence (+, More than one +)) and following classes for creatinine clearance (severe, mild, moderate, normal) and using shift tables from baseline to the worst (high and/or low) and last class or value under treatment will be described.

Some parameters with grade dependent on baseline value cannot be computed if there is no value at baseline.

### 3.5.4. Vital signs, clinical examination and other observations related to safety

Vital signs and clinical examination will be described in the SS, in terms of quantitative values for Weight (Kg), and Temperature (°C) and by classes for ECOG, BSA ($m^2$), Heart Rate - HR (bpm), Supine Systolic Blood Pressure - SBP (mmHg), Supine Diastolic Blood Pressure - DBP (mmHg), Respiratory rate (breaths/min), and Oxygen saturation (%):

- ECOG (0, 1, 2, 3, 4) documented in the e-CRF.
- BSA (< 1.07, [1.07,1.23), [1.23, 1.38), [1.38, 1.53), [1.53, 1.69), [1.69, 1.84), [1.84, 1.99), [1.99, 2.15), [2.15, 2.30), ≥ 2.30).
- HR (< 60, [60, 100), ≥ 100 bpm).
- SBP (< 90, [90, 140), ≥ 140 mmHg).
- DBP (< 60, [60, 90), ≥ 90 mmHg).
- Respiratory rate (< 12, [12, 18], > 18 breaths/min).
- Oxygen saturation (< 90, [90, 95], > 95 %).

Vital signs and clinical examination will be described, in terms of value at baseline, value at cycle 1 (worst value) under treatment, worst value under treatment and last post-baseline value under treatment; as well as in terms of change from baseline to cycle 1 (worst value) under treatment, to worst value under treatment, to last post-baseline value under treatment.

### 3.5.5. ECG

The frequency distribution (n, %) of patients with an ECG performed will be described. ECG parameters, as well as heart rate (bpm) (< 60, [60, 100), ≥ 100), will be described by classes, in terms of value at baseline and last post-baseline value under treatment. Moreover values and changes from baseline of uncorrected and corrected (Fridericia's correction ($QTcF = QT/2\sqrt{RR}$)) QT intervals, RR interval, PR interval and QRS duration will also be described in classes, considering the thresholds defined in **7.5**:
≤ 450, (450, 480], (480, 500] and > 500 msec for values.
≤ 30, (30, 60] and > 60 msec for changes.

## 3.6. QoL

Not applicable

# 4. INTERIM ANALYSIS

Not applicable.

# 5. APPENDIX A: DATA HANDLING AND PROGRAMMING SPECIFICATIONS

## 5.1. General analytic definitions

### 5.1.1. Expressions

**Reliable value** for biological and coagulation samplings is identified in datasets with flag BIOFG_*parameter name* ("Non analysable value") different from 1 and non-missing result. For other panels, **reliable value** is a non-missing result.

**Value at baseline** is defined as the last reliable value prior to treatment intake.
Note: In case of patient included and/or randomised but not treated (*i.e.* patients with treatment duration equal to 0): value at baseline is defined as the last reliable value.

**Post-baseline value** is defined as a reliable value after the first study treatment intake.

**Last value** is defined as the last reliable post-baseline value of the criteria of interest during treatment period.

**Withdrawal value** is defined as the reliable value of the criteria of interest during the withdrawal visit.

**Lowest value** is defined as the lowest value during the treatment period.

**Highest value** is defined as the highest value during the treatment period.

**Worst (lowest/highest) value at cycle *i*** is defined as the worst (lowest/highest) value at cycle.

### 5.1.2. Value prior to treatment / under treatment

**Table (5.1.2) 1 - Time frame**

| Criteria | Value prior to treatment if measured between (D1 =) days before and (D2 =) days after the first treatment intake (D1 and D2 included) | | Post-baseline value on studied/interest period if measured between (D1 =) days after the first treatment intake and until (D2 =) days after the last treatment intake as defined in Section 5.1.5 (D1 and D2 included) | |
|---|---|---|---|---|
| Tumour assessment (all lesions) | D1 = 28 | D2 = Xsup | D1 = Xinf | D2 = 30 |
| Biochemistry/haematology/ coagulation/urinanalysis | D1 = 7 | D2 = Xsup* | D1 = Xinf* | D2 = 30 |
| Vital signs and physical examinations | D1 = 7 | D2 = Xsup* | D1 = Xinf* | D2 = 30 |
| Pregnancy test | D1 = 7 | D2 = Xsup | D1 = NA | D2 = NA |
| ECG | D1 = 28 | D2 = Xsup | D1 = Xinf | D2 = 30 |
| Concomitant treatment | D1 = -∞ | D2 = Xsup | D1 = Xinf | D2 = 0 |
| AE expected | D1 = -∞ | D2 = Xsup | D1 = Xinf | D2 = 30 |

*Xsup: 0 and" Visit< "C001"*
*Xsup*: 0 and" Visit≤ "C001" where DAY ≠ unscheduled*
*Xinf: 0 and" Visit ≥ "C001"*
*Xinf*: 1 and" Visit ≥ "C001",(Note: C001 DAY = unscheduled is considered as a post-dose assessment when reported the same date as the first treatment intake)*

**Table (5.1.2) 2 - Time frame of cycle n**

| Notations | Definitions |
|---|---|
| Cycle n | Start date: First IMP intake date of cycle n<br><br>End date: The day before the 1st IMP intake of cycle (n+1)<br>➢ It means that assessments planned the same day but before the 1st IMP intake in cycle (n+1) are part of cycle n.<br>For the last cycle, End date = min (first IMP intake date, date of death).<br><br>(*)<br>max (first intake date of trifluridine/tipiracil of last cycle + 27 days, first intake date of futuximab/modotuximab of last cycle + 27 days) The Data Management variable VISIT in exposure dataset will be used to determine the start date of each cycle. |

### 5.1.3. General duration derivation and conversion

In instances where duration or time-to-event is calculated, the convention to be used unless otherwise specified is [later date] – [earlier date] + 1 day.

When converting a number of days to other units, the following conversion factors will be used: 1 year = 365.25 days; 1 month = 30.44 days.

### 5.1.4. Analysable value

**Table (5.1.4) 1 - Definition of analysable value**

| **General definition** | |
|---|---|
| Non missing value | |
| | |
| **Specific definitions** | |
| Laboratory parameters | Only reliable values are considered for analyses. Unreliable values are flagged into the database. |
| ECG parameters | For the analysis of QT criteria per measurement time, only scheduled values will be analyzed. |

### 5.1.5. First and last IMP intake dates

For patients having taken at least one dose of IMP, the dates of first and last IMP intake on the analysis period will be defined as follows:

- The date of the first IMP intake = min (first trifluridine/tipiracil intake date, first futuximab/modotuximab infusion date) within the analysis period.
- The date of the last IMP intake = max (last trifluridine/tipiracil intake date, last futuximab/modotuximab infusion date) within the analysis period.

After selection of the dates of first and last IMP intake as defined above, if these dates are missing or incomplete, the following substitution rules will be applied:

**Table (5.1.5) 1 - Substitution rules of tIMP intake dates**

| **Date to substitute** | | **Substituted date** |
|---|---|---|
| First IMP intake | ../mmm/yyyy | Inclusion date* if complete with same month and year<br>*Otherwise*<br>**01/mmm/yyyy** |
| | ../…/yyyy | Inclusion date* if complete with same year<br>*Otherwise*<br>**01/JAN/yyyy** |
| | ../.../…. | Inclusion date*if totally incomplete |
| Last IMP intake | ../mmm/yyyy | **Last available date**** if same month and year<br>*Otherwise*<br>**last day of the month/mmm/yyyy** |
| | ../…/yyyy | **Last available date**** if same year<br>*Otherwise*<br>**31/DEC/yyyy** |
| | ../.../…. | **Last available date**** |

*Notes:*

- *Missing dates will be substituted only for patients having taken at least one dose of study treatment*
  *../mmm/yyyy = missing day*
  *../.../ yyyy = missing day and month*
  *../.../.... = totally missing date*
- ** inclusion date (or dispensation date if inclusion date is missing)*
- *** Last available date (only for patients included) is defined as date of death if patient died, and as maximum date among completed dates relative to patient's information otherwise.*
-

*Note:*

*Cycles with both missing first and last IMP intake dates and with number of returned tablets equal to number of tablets delivered at the previous cycle (or with estimated number of tablets taken equal to 0) will not be taken into account.*

### 5.1.6. Other dates

The rules for substitution of missing or incomplete death date are as follows:

**Table (5.1.6) 1 - Substitution rules of death date**

| Date to substitute | | Substituted date |
|---|---|---|
| Death date | ../mmm/yyyy | **Last available date*** if same month and year<br>*Otherwise*<br>**01/mmm/yyyy** |
| | ../.../yyyy | **Last available date*** if same year<br>*Otherwise*<br>**01/JAN/yyyy** |
| | ../.../.... | **No substitution** |

*Notes:*

*../mmm/yyyy = missing day*
*../.../ yyyy = missing day and month*
*../.../.... = totally missing date*

- ** Last available date is defined as maximum date among completed dates relative to patient's information otherwise.*

If no specific management of dates is defined, missing information is substituted as defined below:

**Table (5.1.6) 2 - Substitution rules of dates if no specific management is defined**

| Date to substitute | | Substituted date |
|---|---|---|
| Date | ../mmm/yyyy | 01/mmm/yyyy |
| | ../.../yyyy | 01/JAN/yyyy |
| | ../.../.... | No substitution |

*Note:*
*../mmm/yyyy = missing day*
*../.../ yyyy = missing day and month*
*../.../.... = missing date*

## 5.2. Specific analytic definitions and data handling conventions

### 5.2.1. Study patients: Disposition, baseline characteristics and follow-up

#### 5.2.1.1. Disposition of patients

All treatment withdrawal reasons occurred in the study will be taken into account (adverse event, protocol deviation, progressive disease (radiological progressive disease, clinical progressive disease, radiological and clinical progressive disease), non-medical reason (consent withdrawal from study treatment, consent withdrawal including survival follow-up), lost to follow-up, physician decision or other medical reason).

#### 5.2.1.2. Protocol deviations

Deviation categories have been defined in order to gather all the deviations relative to the same topic.

For the description of protocol deviations, the 6 following categories are considered in accordance with ICH E3 guideline and ICH E3 Q&A:

- Selection/inclusion criteria not fulfilled.
- Patient having withdrawal criteria but not withdrawn.
- Incorrect treatment or dose received.
- Forbidden concomitant treatment.
- Endpoint assessment possibly affected.
- Safety possibly affected.

#### 5.2.1.3. Demographic data and other baseline characteristics

##### 5.2.1.3.1. Demographic data

**Age** is calculated as difference between year of informed consent and year of date of birth.

##### 5.2.1.3.2. History of Colorectal cancer

**Primary tumour localisation:**

- **Right** if primary tumour site = right colon(1) or transverse or other*
- **Left** if primary tumour site = left colon(2) or rectum

*(1) Right colon should include multilocalised right colon, ascending colon, cecum, appendix and hepatic flexure.*
*(2) Left colon should include multilocalised left colon, descending colon, sigmoid colon, splenic flexure and rectosigmoid segment.*
**Other: in the case the patient present multiple tumours in both sides, the disease will be considered as "right-sided".*

**Site of metastasis** is defined from History of colorectal cancer e-CRF page.

**Number of metastatic site** is defined as the number of distinct site of metastasis (whether the site is considered for target or non-target lesion) from History of colorectal cancer e-CRF page. Sites filled in 'Other' will be counted as 1 site.

**Disease duration**
Disease duration (years) is defined as (Inclusion date – date of the first diagnosis of colorectal cancer)/365.25

**Time from first metastasis diagnosis to inclusion**
Time from first metastasis diagnosis to inclusion (months) is defined as (inclusiondate – first metastasis diagnosis date)/30.44

**Progression free interval**
Progression free interval (months) is defined as (Date of progression prior to the randomisation date – date of end of the last prior anti-cancer therapy*)/30.44.

The progression free interval of patients progressing during the last regimen is estimated to last one day.
**Including drug treatment, radiotherapy and surgery (whatever the intent).*

**Treatment free interval**
Treatment free interval (months) is defined as (date of first IMP intake – date of end of the last prior anti-cancer therapy*)/30.44.
**Including drug treatment, radiotherapy and surgery.*

Of note, in case of partial or incomplete date:

**Table (5.2.1.3.2) 1 - Substitution rules of History of colorectal cancer**

| **Missing diagnosis date** | | **Substituted diagnosis date** |
|---|---|---|
| ../mm/yyyy | ⇨ | Diagnosis date = **01**/mm/yyyy |
| ../…/yyyy | ⇨ | Diagnosis date = **01/01**/yyyy |
| **Missing metastasis date** | | **Substituted metastasis date** |
| ../mm/yyyy | ⇨ | Metastasis date = **01**/mm/yyyy |
| ../…/yyyy | ⇨ | Metastasis date =**01/01**/yyyy |
| **Missing start date of the last prior therapy** | | **Substituted start date of the last prior therapy** |
| ../mm/yyyy | ⇨ | start date of the last prior therapy = **01**/mm/yyyy |
| ../…/yyyy | ⇨ | start date of the last prior therapy = **01/01**/yyyy |
| **Missing end date of the last prior therapy** | | **Substituted end date of the last prior therapy** |
| ../mm/yyyy | ⇨ | end date of the last prior therapy = start date of the last prior therapy + 1day if same month and year<br>*otherwise*:<br>end date of the last prior therapy = 01/mm/yyyy |
| ../…/yyyy | ⇨ | end date of the last prior therapy = start date of the last prior therapy + 1day if same year<br>*otherwise*:<br>end date of the last prior therapy = 01/01/yyyy |
| ../…/… | ⇨ | end date of the last prior therapy = start date of the last prior therapy + 1day |
| **Missing start date of a previous treatment** | ⇨ | **Substituted start date of a previous treatment** |
| ../mmm/yyyy | ⇨ | 01/mmm/yyyy |
| ../…/yyyy | ⇨ | 01/JAN/yyyy |
| ../.../…. | ⇨ | Inclusion date |

*Note: ../mm/yyyy = missing day*
*../.../ yyyy = missing day and month*
*../.../.... = missing date*

## RAS status

**Table (5.2.1.3.2) 2 - RAS status**

| **KRAS** | **NRAS** | **RAS** |
|---|---|---|
| MUTANT | whatever (mutant, wild, missing) | MUTANT |
| whatever (mutant, wild, missing) | MUTANT | MUTANT |
| WILD | WILD | WILD |
| MISSING | WILD | NE |
| WILD | MISSING | NE |
| MISSING | MISSING | NE |

## Stage at diagnosis

**Table (5.2.1.3.2) 3 - Staging based on classification**

| **Stage in classes** | **AJCC stage** | **Dukes' classification** | **Astler-Coller modified Dukes' classification** |
|---|---|---|---|
| | **Stage 0** | - | - |
| **I-II** | **Stage I** | A | A |
| **I-II** | **Stage I** | A | B1 |
| **I-II** | **Stage II-A** | B | B2 |
| **I-II** | **Stage II-B** | B | B2 |
| **I-II** | **Stage II-C** | B | B3 |

| | | | |
|---|---|---|---|
| **III** | **Stage III-A** | C | C1 |
| | **Stage III-B** | C | C2 |
| | | C | C1/C2 |
| | | C | C1 |
| | **Stage III-C** | C | C2 |
| | | C | C2/C3 |
| | | C | C3 |
| **IV** | **Stage IV-A** | | D |
| | **Stage IV-B** | | |
| | **Stage IV-C** | | |

#### 5.2.1.3.3. Previous therapies for colorectal cancer

**The existence of a previous drug treatment** (Yes, No) is defined from the presence, or not of an "anatomical therapeutic chemical classification" and/or a "preferred name" for the previous drug treatment at inclusion visit.

**The existence of a previous metastatic drug treatment** (Yes, No) is defined from the presence, or not of an "anatomical therapeutic chemical classification" and/or a "preferred name" for the previous drug treatment after the date of 1st metastasis.

**The existence of a previous adjuvant drug treatment** (Yes, No) is defined from the presence or not of a previous drug treatment with an adjuvant indication.

**The existence of a previous neoadjuvant drug treatment** (Yes, No) is defined from the presence or not of a previous drug treatment with a neoadjuvant indication.

**The existence of a previous fluoropyrimidine drug treatment (Yes, No)** is defined from the presence, or not of a previous drug treatment belonging to the list 3678.0.

**The existence of a previous irinotecan drug treatment (Yes, No)** is defined from the presence, or not of a previous drug treatment belonging to the list 3674.0.

**The existence of a previous oxaliplatin drug treatment (Yes, No)** is defined from the presence, or not of a previous drug treatment belonging to the list 3675.0.

**The existence of a previous anti-VEGF monoclonal antibody drug treatment (Yes, No)** is defined from the presence, or not of a previous drug treatment belonging to the list 4281.0.

**The existence of a previous anti-EGFR monoclonal antibody drug treatment (Yes, No)** is defined from the presence, or not of a previous drug treatment belonging to the list 4280.0.

**Number of prior regimens for mCRC** is calculated as the sum of previous drug treatments for mCRC except if reported in a maintenance indication.

**The duration of previous metastatic regimen containing anti-EGFR monoclonal Anti Body (months)** is defined as (last previous anti-EGFR monoclonal Anti Body drug treatment end date – first previous anti-EGFR monoclonal Anti Body drug treatment start date)/30.44.

#### 5.2.1.3.4. Initial tumour assessment

Not applicable.

#### 5.2.1.4. Extent of exposure and treatment compliance

**Treatment duration for trifluridine/tipiracil**
Treatment duration (months) for trifluridine/tipiracil is defined as ([min (first intake date of the last cycle + 27 days**,** death date) - first trifluridine/tipiracil intake date] +1)/30.44.

**Treatment duration for futuximab/modotuximab**
Treatment duration (months) for futuximab/modotuximab is defined as [(min (first infusion date of the last cycle + 27 days, death date) - first futuximab/modotuximab infusion date) +1] / 30.44.

For trifluridine/tipiracil and futuximab/modotuximab, in case of missing or incomplete first intake date of the last cycle, the last intake date of the last cycle will be considered.

**Cycle duration for trifluridine/tipiracil**
Duration of cycle *i* (weeks) for trifluridine/tipiracil is defined as [[first trifluridine/tipiracil intake of cycle (*i+1*)] – [first trifluridine/tipiracil intake of cycle *i*]] / 7.

Of note, the duration of the last cycle for trifluridine/tipiracil will be estimated to be 28 days for the calculation of Dose Intensity and Relative Dose Intensity at the last cycle.

**Cycle duration for futuximab/modotuximab**
Duration of cycle *i* (weeks) for futuximab/modotuximab is defined as [[first futuximab/modotuximab infusion of cycle (*i+1*)] – [first futuximab/modotuximab infusion of cycle *i*]] / 7.

Of note, the duration of the last cycle for futuximab/modotuximab will be estimated to be 28 days for the calculation of Dose Intensity and Relative Dose Intensity at the last cycle.

**Follow-up duration**
The follow-up duration (months) is calculated as the duration between the last available date and the inclusion date [last available date* – inclusion date +1]/30.44. The events of interest are being alive or lost to follow-up and death is censored.
** Last available date is defined as date of death if patient died, and as maximum date among completed dates relative to patient's information otherwise.*

**Number of cycles for trifluridine/tipiracil**
The number of cycles with trifluridine/tipiracil will be defined based on trifluridine/tipiracil administration page. A patient is considered to enter in a cycle if there is at least one answer 'Yes' to the question 'Has the patient taken his/her morning (or evening) intake?'.

**Real administrated dose (mg) for trifluridine/tipiracil**
On a time period, real administered dose for trifluridine/tipiracil (mg) = Number of capsules 15 mg taken*15 + Number of capsules 20 mg taken*20
With:

- Number of capsules taken = Number of capsules dispensed - Number of capsules returned

Else, if Number of capsules returned is missing, Number of capsules taken = Estimated number of capsules taken.

**Number of cycles for futuximab/modotuximab**

The number of cycles with futuximab/modotuximab will be defined based on futuximab/modotuximab administration page. A patient is considered to enter in a cycle if the answer is "Yes" to the question "Did the patient receive the IMP infusion?'.

**Real administrated dose (mg) for futuximab/modotuximab**
On a time period, real administered dose for futuximab/modotuximab (mg) = sum of total dose administrated (full + incomplete doses).
In case of incomplete dose administered, the real dose administered can be computed as: planned dose to be given (mg) * actual volume administered (mL) / infusion volume planned (mL)

**Planned dose intensity (PDI) for trifluridine/tipiracil (mg/m²/week)**

| | **10 days of intake per cycle** |
|---|---|
| **35** mg/m² **(bid)** (**70** mg/m²/day) | $\frac{\mathbf{70}(\mathrm{mg/m^2/day}) * \mathbf{10}}{4\ (\mathrm{wk})}$ |

**Planned dose intensity (PDI) for futuximab/modotuximab (mg/kg/week)**

| | **4 weeks of infusion per cycle** |
|---|---|
| **9 mg/kg (the first week) then 6 mg/kg (weekly)** for cycle 1 | $\frac{\mathbf{9}(\mathrm{mg/kg/week}) + \mathbf{6}(\mathrm{mg/kg/week}) * \mathbf{3}}{4\ (\mathrm{wk})}$ |
| **6 mg/kg (weekly)** for next cycles | $\frac{\mathbf{6}(\mathrm{mg/kg/week}) * 4}{4\ (\mathrm{wk})}$ |

**Cumulative dose**
The cumulative dose (mg/m²*)* for trifluridine/tipiracil per patient in a time period (during the treatment period or per cycle) is the sum of the total dose that the patient received within that period according to the compliance.

$$Cumulative\ dose\ (mg/m^2) = \sum_{timeperiod} \left( \frac{Real\ Administrated\ dose\ (mg)}{BSA\ (m^2)} \right)$$

Where BSA is calculated in the ClinTrial database by the data management.

The cumulative dose (mg/kg*)* for the futuximab/modotuximab per patient in a time period (during the treatment period or per cycle) is the sum of the total dose that the patient received within that period according to the compliance.

$$Cumulative\ dose\ (mg/kg) = \sum_{timeperiod} \left( \frac{Real\ Administrated\ dose\ (mg)}{weight\ (kg)} \right)$$

**Dose intensity (DI) per patient**
The dose intensity (mg/m²/week) for trifluridine/tipiracil per patient is defined as the cumulative dose (mg/m²*)* received during the treatment period divided by the total treatment duration in weeks.

$$DI\ (mg/m^2/wk)\ per\ patient\ = \frac{Cumulative\ dose\ (mg/m^2)}{Treatment\ duration\ (weeks)}$$

The dose intensity (mg/kg/week) for the futuximab/modotuximab per patient is defined as the cumulative dose (mg/kg) received during the treatment period divided by the total treatment duration in weeks.

$$DI\ (mg/kg/wk)\ per\ patient\ = \frac{Cumulative\ dose\ (mg/kg)}{Treatment\ duration\ (weeks)}$$

**Dose intensity (DI) per cycle**

The dose intensity (mg/m²/week) for trifluridine/tipiracil per cycle is defined as the cumulative dose (mg/m²) received during the cycle divided by the cycle duration in weeks.

$$DI\ (mg/m^2/wk)\ at\ cycle\ i\ = \frac{Cumulative\ dose\ (mg/m^2)\ received\ at\ cycle\ i}{Duration\ of\ cycle\ i\ (weeks)}$$

The dose intensity (mg/kg/week) for the futuximab/modotuximab per cycle is defined as the cumulative dose (mg/kg) received during the cycle divided by the cycle duration in weeks.

$$DI\ (mg/kg/wk)\ at\ cycle\ i\ = \frac{Cumulative\ dose\ (mg/kg)\ received\ at\ cycle\ i}{Duration\ of\ cycle\ i\ (weeks)}$$

**RDI per patient**

The RDI (%) per patient is defined as the ratio of the DI to the initial PDI.

$$RDI\ (\%)\ per\ patient\ = \frac{DI}{Planned\ dose\ intensity} * 100$$

**RDI per cycle**

The relative dose intensity (%) per cycle is defined as the ratio of the dose intensity at cycle i to the planned dose intensity.

$$RDI\ (\%)\ at\ cycle\ i\ = \frac{DI\ at\ cycle\ i}{Planned\ dose\ intensity} * 100$$

**Dose reduction for trifluridine/tipiracil**

A cycle with a dose reduction is defined according to the trifluridine/tipiracil dispensing e-CRF page (dose modified since the last cycle (Yes, No)).

**Partial dose administered for futuximab/modotuximab**

Partial dose administered for the futuximab/modotuximab is defined by an answer “No” at the eCRF interrogation “Was full dose administered?”.

**Dispensation postponed for trifluridine/tipiracil**

A cycle with a dispensation postponed is defined according to the trifluridine/tipiracil dispensing e-CRF page (Dispensation postponed (Yes, No)).

**Unplanned treatment interruption for trifluridine/tipiracil**

A treatment interruption is defined according to the number of days between two consecutive dates where the answer is ‘Yes’ to the questions ‘Has the patient taken his/her morning intake’ or ‘Has the patient taken his/her evening intake’ when this duration is one day or longer considering trifluridine/tipiracil administration schedule (5 days on/2 days off, over 14 days followed by a 14-day rest).

Treatment interruption (days) = (date with an answer 'Yes' to the questions 'Has the patient taken his/her morning intake' or 'Has the patient taken his/her evening intake' – following date with an answer 'Yes' to the questions 'Has the patient taken his/her morning intake' or 'Has the patient taken his/her evening intake') -1

Note: only intra-cycle interruptions will be considered

#### 5.2.1.5. Concomitant treatments

**The anatomical therapeutic chemical classification** (ATC code = 5 digits) is composed of 4 levels:

- The first (1 digit) represents the anatomo-physiological class.
- The second (2 digits) represents the pharmacological class.
- The third (1 digit) represents the pharmacological sub-class.
- The last (1 digit) represents the therapeutic class.

**The existence of a concomitant treatment** (Yes, No) is defined from the presence, or not, of an Anatomical therapeutic chemical classification and/or Preferred name.

The **periods** considered **for the analysis** are:
At inclusion for which treatments:

- With start date ≤ inclusion date and stop date ≥ inclusion date or missing are taken into account. Inclusion date is equal to the date of inclusion visit, *i.e.* A000/D000 visit date.

Before the treatment period for which treatments:

- With start date < first IMP intake date are taken into account.

During the treatment period for which treatments:

- With start date ≥ first IMP intake date and < (*), or
- With start date ≤ first IMP intake date and stop date ≥ first IMP intake date or missing

After the treatment period for which treatments:

- With start date ≥ (*), or
- With start date ≤ (*) and stop date > (*) or missing.

*(*)max (first intake date of last cycle + 28 days of trifluridine/tipiracil, first intake date of last cycle + 28 days of futuximab/modotuximab)*

The following **rules for substitution** of missing or incomplete start and stop dates are so that the concomitance period is maximised:

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

**Table (5.2.1.5) 1 - Substitution rules of concomitant treatments intake dates**

| **Date to substitute** | | **Substituted date** |
|---|---|---|
| Start date | ../mmm/yyyy | If the year and the month are the same as the year and the month of inclusion then<br>Start date = **Inclusion date,**<br><br>otherwise<br>Start date = **01/mm/yyyy** |
| | ../…/yyyy | If the year is the same as the year of inclusion then<br>Start date = **Inclusion date,**<br><br>otherwise<br>Start date = **01/01/yyyy** |
| | ../.../…. | If stop date is non-missing and inferior to inclusion date then:<br>**Stop date**<br>Else:<br>**Inclusion date** |
| Stop date | ../mmm/yyyy | If patient died same month and year then<br>**Date of death**<br>Else<br>**Last day of the month/mmm/yyyy** |
| | ../…/yyyy | If patient died same year then<br>**Date of death**<br>Else<br>**31/DEC/yyyy** |
| | ../.../…. | If patient died then<br>**Date of death**<br>Else<br>**No substitution**<br>(*i.e.,* treatment considered as still ongoing) |

*Note: ../mm/yyyy = missing day*
*../.../yyyy = missing day and month*
*../.../.... = missing date*

The following rules for substitution of totally or partially missing start and stop dates are used for concomitant treatments (only further anti-tumour therapy):

**Table (5.2.1.5) 2 - Substitution rules of further anti-tumour therapy intake dates**

| Date to substitute | | Substituted date |
|---|---|---|
| Start date | ../mmm/yyyy | If the year and the month are the same as the year and the month of the last IMP intake date then<br>**Last IMP intake date**<br><br>otherwise<br>**01/mm/yyyy** |
| | **../…/yyyy** | If the year is the same as the year of the last IMP intake date then<br>**Last IMP intake date**,<br><br>otherwise<br>**01/01/yyyy** |
| | ../.../…. | **Last IMP intake date** |
| Stop date | ../mmm/yyyy | If patient died same month and year then<br>**Date of death**<br>Else<br>**Last day of the month/mmm/yyyy** |
| | **../…/yyyy** | If patient died same year then<br>**Date of death**<br>Else<br>**31/DEC/yyyy** |
| | ../.../…. | If patient died then<br>**Date of death**<br>Else<br>**No substitution**<br>(*i.e.,* treatment considered as still ongoing) |

*Note: ../mm/yyyy = missing day*
*../.../ yyyy = missing day and month*
*../.../.... = completely missing date*
*The last IMP intake corresponds to the real last IMP intake within the analysis period.*

# 6. APPENDIX B: EFFICACY

## 6.1. Non-confirmed Best overall response

Best overall response is defined as the best overall response across all time points excluding "Follow-up" e-CRF information. If applicable, responses recorded after intercurrent events will be excluded.

When SD is believed to be best overall response, it needs to be assessed a minimum of 6 weeks after study inclusion. Otherwise, the best overall response will be NE, unless any PD was further documented, in which case BOR will be PD.

A patient dead because of progression* before the first assessment planned per protocol (8 weeks) will be considered as 'early death'. If a patient progressed* before this first assessment, he will be considered as 'early progressive'. If any of these two events occur, the overall response of the patient will be resumed as progression (PD).

**: Progression/Death due to progression before the end of cycle 2:*
*According to tumoral evaluation.*
*Withdrawal reason status.*

In case of best overall response missing under the studied period, this one will be considered as Non-Evaluable (NE).

Complete response (CR) and partial response (PR) will not be confirmed following initial documentation of overall response.

**Table (6.1) 1 - BOR when confirmation of CR and PR not required**

| Overall response<br>First time point (i) | Overall response<br>Next time point (i+1) | BOR |
|---|---|---|
| CR | Whatever the overall response | CR |
| PR | Whatever the overall response other than CR | PR |
| SD | PD | SD (if the time length between the study inclusion and the SD is ≥ 6 weeks), otherwise, PD |
| SD | SD or NE or missing | SD (if the time length between the study inclusion and one of the SD is ≥ 6 weeks), otherwise, NE unless any PD was further documented |
| PD | Whatever the overall response | PD |
| NE or missing | PD | PD |
| NE or missing | NE or missing | NE |

# 7. APPENDIX C: SAFETY

The **periods** considered **for the analysis** of adverse events, deaths and clinical laboratory evaluation are:

- During the treatment period:
  - With date ≥ first IMP intake date and <=last IMP intake date as defined in the Section 5.1.5 + 30 days.
- After the treatment period:
  - With date > last IMP intake date as defined in the Section 5.1.5 + 30 days.

## 7.1. Adverse events

Each **medical concept of adverse events coded according to the internal "multiple medical concept" process** is taken into account as a single adverse event in the statistical analysis.

The modalities of the adverse event (onset and end dates, severity, seriousness, action taken, additional therapy, relationship, outcome...) replicated by default to each medical concept are also taken into account in the statistical analyses.

**Emergent adverse events on treatment are defined as all adverse events:**

- Which occur between the first IMP intake date (included) and the last IMP intake date "+ 30 days″ (included), considering the definition of last study drug intake defined in Section 5.1.5

or

- Which occur before the first IMP intake date and which worsen (in terms of severity) or become serious according to the investigator opinion between the first IMP intake date (included) and the last IMP intake date "+ 30 days″ (included), considering the definition of last study drug intake defined in Section 5.1.5.

Note: Adverse events occurring or worsening or becoming serious on the day of the first study drug/associated agent intake (if any) is considered as emergent.

Serious adverse events are defined from investigator assessment as all adverse events fulfilling at least one of the following seriousness criteria for immediate notification: death, hospitalisation or prolongation of hospitalisation, medically important, life-threatening, disability/incapacity or congenital anomaly.

**A fatal adverse event** corresponds to an adverse event with “Fatal” as outcome.

**Adverse events related to Trifluridine/tipiracil** correspond to adverse events associated with the answer "Related" to the "Is this event related to Trifluridine/tipiracil" question.

**Adverse events related to Futuximab/modotuximab** correspond to adverse events associated with the answer "Related" to the "Is this event related to Futuximab/modotuximab" question.

**Adverse events related to the combination** correspond to adverse events associated with the answer "Related" to the "Is this event related to Trifluridine/tipiracil " question and/or with the answer "Related" to the "Is this event related to Futuximab/modotuximab" question.

**Adverse events related to disease progression** correspond to adverse events associated with the answer "Related" to the "Is this event related to disease progression" question.

The following information will be taken into account:

- For the analyses where the severity of the adverse event is considered, the worst severity from the day of emergence and during the studied period (*i.e.* between the first study drug/associated agentintake date (included) and the last study drug/associated agent intake date (as defined in Section 5.1.5) "+ 30 days" (included) will be taken into account.
- The number of patients by worst grade: for each patient, system organ class and preferred term, we analyze the worst grade of events.
- The number of events by worst grade: for each patient, system organ class and preferred term, we analyse the worst grade of each event. The percentage will be calculated as the number of events of the PT concerned at grade X divided by the total number of events of the PT concerned.
- For the analyses where the action taken regarding the study drug and the additional therapy requirement are considered, all the actions taken and additional therapy requirements recorded from the day of emergence and on the studied period will be taken into account.
- However, in case of an episode of an emergent adverse event leading to studied treatment withdrawal reported after the last study drug/associated agent intake date (as defined in Section 5.1.5) "+ 30 days", the adverse event will be considered as leading to studied treatment withdrawal during the studied period.
- Seriousness is judged by event: if one episode is serious (whatever the time it occurs), the whole event will be considered as serious.
- A severe adverse event corresponds to an adverse event with NCI CTCAE grade 3, 4 or 5.
- Any grade corresponds to an adverse event with NCI CTCAE grade 1, 2, 3, 4 or 5.
- All multicoded events will be taken into account in the analyses.
- For the analysis of recovered emergent adverse event during / after treatment period, a TEAE is considered as recovered "during treatment period" ("after end of treatment period", respectively) if the associated outcome is recovered" or "recovered with sequelae" and occurs between the first study drug/associated agent intake date and the last study drug/associated agent intake date (as defined in Section 5.1.5) "+ 30 days" (included) (strictly after the last study drug/associated agent intake date (as defined in Section 5.1.5) "+ 30 days", respectively).

The following rules are applied in case of missing severity:

**Table (7.1) 1 - Treatment-emergence of adverse events in case of missing severity/grade (if any)**

| Severity/Grade | | | Adverse event considered as |
|---|---|---|---|
| **Nearest before the first study drug/associated agent intake date** | **During the study period** | | |
| Missing | Missing | → | Treatment-emergent |
| Missing | Grade 1 | → | Non treatment-emergent |
| Missing | Grade 2, 3, 4 or 5 | → | Treatment-emergent |
| Grade 1, 2, 3 | Missing | → | Treatment-emergent |
| Grade 4 | Missing | → | Non treatment-emergent |

The rules for substitution of missing or incomplete episode date (onset date, dates of the *six* seriousness criteria and dates of change of severity and action taken) are as follows:

**Table (7.1) 2 - Substitution rules of AE dates**

| Date to substitute | Substituted date (Episode date) |
|---|---|
| ../mmm/yyyy | If same month and year than first study drug/associated agent intake date then:<br>**First study drug/associated agent intake date**<br>Else:<br>**01/mmm/yyyy** |
| • ../…/yyyy | If same year than first study drug/associated agent intake date then:<br>**First study drug/associated agentintake date**<br>Else:<br>**01/JAN/yyyy** |
| • ../…/…. | **First study drug/associated agent intake date** |

*Note: ../mm/yyyy = missing day*
*../.../ yyyy = missing day and month*
*../.../.... = missing date*

The rules for substitution of missing or incomplete recovery dates, in case of AE outcome "recovered" or "recovered with sequelae" are as follows:

**Table (7.1) 3 - Substitution rules of recovery date**

| Date to substitute | Substituted date |
|---|---|
| ../mmm/yyyy | If same month and year than date of AE last information(*) then:<br>**Date of AE last information**<br>Else:<br>**Last day of the month /mmm/yyyy** |
| ../…/yyyy | If same year than date of AE last information(*) then:<br>**Date of AE last information**<br>Else:<br>**31/DEC/yyyy** |
| ../…/…. | **Date of AE last information(*)** |

*Notes:*
- *../mmm/yyyy = missing day,*

*../.../ yyyy = missing day and month,*
*../.../.... = missing date.*
*(*) Date of AE last information is defined as the maximum between onset date, dates of change of severity and action taken and dates of the six seriousness criteria for this adverse event.*

## 7.2. Death

Death information are taken on 'Adverse Event' (serious criteria for immediate reporting = Death) and 'Status of the patient at follow-up X' (reason for not continuing the follow-up period = Death) e-CRF pages.

In case of death reported on 'Adverse Event' page, the date of death is compared to the date of last intake (as defined in Section 5.1.5) "+ 30 days" to classify occurrence on-treatment or during follow-up.

## 7.3. Clinical laboratory evaluation

**Values**
Only reliable values are considered for analyses. Unreliable values are flagged into the database.

In case of **multiple samples**:

- For the description of the values at each planned post-baseline visit, only the first analysable one measured under treatment at the visit is taken into account.
- Otherwise, each post-baseline value (test, re-test, planned, unplanned) measured under treatment is taken into account for analyses.

**Units**

All parameters will be analysed in international units (IU).

**Abnormal values**

Abnormal values are described according to:

- Reference laboratory ranges for the non-gradable parameters.
- CTCAE grade for gradable parameters.

**Table (7.3) 1 - Gradable and non-gradable laboratory parameters**

| Laboratory parameters | | Parameter | Highest | Lowest |
|---|---|---|---|---|
| Biochemistry | Gradable | Sodium | Hypernatremia | Hyponatremia |
| Biochemistry | Gradable | Potassium | Hyperkalemia | Hypokalemia |
| Biochemistry | Gradable | Total Calcium | Hypercalcemia | Hypocalcemia |
| Biochemistry | Gradable | Magnesium | Hypermagnesemia | Hypomagnesemia |
| Biochemistry | Gradable | Serum creatinine | High creatinine* | NA |
| Biochemistry | Gradable | Albumin | NA | Low albumin |
| Biochemistry | Gradable | Glucose | Hyperglycemia | Hypoglycemia |
| Biochemistry | Gradable | GGT | High GGT* | NA |
| Biochemistry | Gradable | AST | High AST* | NA |
| Biochemistry | Gradable | ALT | High ALT* | NA |
| Biochemistry | Gradable | Alkaline phosphatase | High alkaline phosphatase* | NA |
| Biochemistry | Gradable | Total bilirubin | High total bilirubin* | NA |
| Haematology | Gradable | Haemoglobin | High haemoglobin* | anemia |
| Haematology | Gradable | White blood cells | NA | Low WBC |
| Haematology | Gradable | Neutrophils | NA | Low neutrophils |
| Haematology | Gradable | Lymphocytes | High lymphocytes | Low lymphocytes |
| Haematology | Gradable | Platelets | NA | Low platelets |
| Coagulation | Non-gradable | Prothrombin Time | High Prothrombin Time | NA |
| Coagulation | Gradable | Activated Partial Thromboplastin Time (aPTT) | High aPTT | NA |
| Biochemistry | Non-gradable | Creatinine clearance** | NA | Low creatinine clearance |
| Biochemistry | Non-gradable | Chloride | High chloride | Low chloride |
| Biochemistry | Non-gradable | Blood urea nitrogen | High urea nitrogen | NA |
| Biochemistry | Non-gradable | LDH | High LDH | NA |
| Biochemistry | Non-gradable | Phosphate | NA | Hypophosphatemia |
| Haematology | Non-gradable | Red blood cells | High RBC | Low RBC |

**: Parameter with grade dependent on baseline value (grade cannot be computed if there is no value at baseline)*
***: Creatinine clearance is calculated in the ClinTrial database (by the data management department) if the data was not reported in the e-CRF.*

Laboratory reference limits and CTCAE grades are reported in the database. Grades directly derived in the database (CTCAE v5.0) will be used for analyses. For the parameters which are gradable according to CTCAE v5.0 and for which the grade is not derived in the database, the grades will be derived using the local laboratory reference limits in analysis datasets.

**Table (7.3) 2 - Definition of CTCAE grade - Version 5.0 - Gradable parameters according to baseline value**

| Parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Sodium (mmol/L) - Hypernatremia | ]ULN;150] | ]150;155] | ]155;160] | >160 |
| Sodium (mmol/L) - Hyponatremia | [130;LLN[ | | [120;130[ | < 120 |
| Potassium (mmol/L) - Hyperkalemia | ]ULN;5.5] | ]5.5;6] | ]6;7] | >7 |
| Potassium (mmol/L) - Hypokalemia | | [3.0;LLN[ | [2.5;3.0[ | <2.5 |
| Total Calcium – Hypercalcemia | ]ULN ; 2.9] | ]2.9 ; 3.1] | ]3.1 ; 3.4] | > 3.4 |
| Total Calcium - Hypocalcemia | [2.0; LLN[ | [1.75;2.0[ | [1.5;1.75[ | < 1.5 |
| Magnesium (mmol/L) - Hypermagnesemia | ]ULN;1.23] | | ]1.23;3.30] | > 3.30 |
| Magnesium (mmol/L) - Hypomagnesemia | [0.5;LLN[ | [0.4;0.5[ | [0.3;0.4[ | <0.3 |
| Serum creatinine increased | >ULN – 1.5 x ULN | >1.5 x baseline – 3.0 x baseline (if baseline available) OR >1.5 x ULN – 3.0 x ULN | >3.0 x baseline (if baseline available) OR >3.0 x ULN – 6.0 x ULN | >6.0 x ULN |
| Albumin (g/L) - Low | [30; LLN[ | [20; 30[ | < 20 | |
| Glucose (mmol/L) - Hypoglycemia | [3.0;LLN[ | [2.2;3.0[ | [1.7;2.2[ | < 1.7 |
| Glucose (mmol/L) - Hyperglycemia | > ULN and > baseline | | | |

| Parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| GGT increased | > ULN – 2.5 x ULN if baseline is normal [≤ ULN]; 2.0 x baseline – 2.5 x baseline if baseline is abnormal [> ULN] | > 2.5 x ULN – 5.0 x ULN if baseline is normal [≤ ULN]; > 2.5 x baseline – 5.0 x baseline if baseline is abnormal [> ULN] | >5.0 x ULN – 20.0 x ULN if baseline is normal [≤ULN]; > 5.0 x baseline – 20.0 x baseline if baseline is abnormal [> ULN] | > 20.0 x ULN if baseline is normal [≤ ULN]; > 20.0 x baseline if baseline is abnormal [> ULN] |
| ASAT increased | > ULN – 3.0 x ULN if baseline is normal [≤ ULN]; 1.5 x baseline – 3.0 x baseline if baseline is abnormal [ > ULN] | > 3.0 x ULN – 5.0 x ULN if baseline is norma [≤ ULN]l; > 3.0 x baseline – 5.0 x baseline if baseline is abnormal [> ULN] | > 5.0 x ULN – 20.0 x ULN if baseline is normal [≤ ULN]; > 5.0 x baseline – 20.0 x baseline if baseline is abnormal [> ULN] | > 20.0 x ULN if baseline is normal [≤ ULN]; > 20.0 x baseline if baseline is abnormal [> ULN] |
| ALAT increased | >ULN – 3.0 x ULN if baseline is normal [≤ULN]; 1.5 x baseline – 3.0 x baseline if baseline is abnormal [ > ULN] | >3.0 x ULN – 5.0 x ULN if baseline is normal[≤ULN]; >3.0 x baseline – 5.0 x baseline if baseline is abnormal [ > ULN] | >5.0 x ULN – 20.0 x ULN if baseline is normal [≤ULN]; >5.0 x baseline – 20.0 x baseline if baseline is abnormal [ > ULN] | >20.0 x ULN x ULN if baseline is normal [≤ULN]; >20.0 x baseline if baseline is abnormal [ > ULN] |
| ALP increased | > ULN – 2.5 x ULN if baseline is normal [≤ ULN]; 2.0 x baseline – 2.5 x baseline if baseline is abnormal [> ULN] | > 2.5 x ULN – 5.0 x ULN if baseline is normal [≤ ULN]; 2.5 x baseline – 5.0 x baseline if baseline is abnormal [> ULN] | > 5.0 x ULN – 20.0 x ULN if baseline is normal [≤ ULN]; > 5.0 x baseline – 20.0 x baseline if baseline is abnormal [> ULN] | > 20.0 x ULN if baseline is normal [≤ ULN]; > 20.0 x baseline if baseline is abnormal [> ULN] |
| Total bilirubin increased | > ULN – 1.5 x ULN if baseline is normal [≤ ULN]; 1.0 x baseline – 1.5 x baseline if baseline is abnormal [> ULN] | >1.5 x ULN – 3.0 x ULN if baseline is normal [≤ ULN]; > 1.5 x baseline – 3.0 x baseline if baseline is abnormal [> ULN] | > 3.0 x ULN – 10.0 x ULN if baseline is normal [≤ ULN]; > 3.0 – 10.0 x baseline if baseline is abnormal [> ULN] | > 10.0 x ULN if baseline is normal [≤ ULN]; > 10.0 x baseline if baseline is abnormal [> ULN] |
| Haemoglobin increased | > ULN and increase from baseline ]0 ;20] (g/L) | > ULN and increase from baseline ]20 ;40] (g/L) | > ULN and increase from baseline > 40 (g/L) | |
| Haemoglobin (g/L) - Anemia | [100;LLN[ | [80;100[ | < 80 | |
| White Blood Cells (G/L) - Low | [3.0;LLN[ | [2.0;3.0[ | [1.0;2.0[ | < 1.0 |
| Neutrophils (G/L) - Low | [1.5;LLN[ | [1.0;1.5[ | [0.5;1.0[ | <0.5 |
| Lymphocytes (G/L) - Low | [0.8;LLN[ | [0.5;0.8[ | [0.2;0.5[ | <0.2 |
| Lymphocytes (G/L) - High | | ]4.0;20.0] | >20 | |
| Platelets (G/L) - Low | [75;LLN[ | [50;75[ | [25;50[ | <25 |
| Prothrombin Time increased | | | | |
| APTT increased | ]ULN;1.5*ULN] | ]1.5*ULN;2.5*ULN] | >2.5*ULN | |
| CREATCLR increased | [60;LLN[ | [30;60[ | [15;30[ | < 15 |

**Any grade** corresponds to a laboratory value with NCI CTCAE grade 0, 1, 2, 3 or 4.

**A grade 0** corresponds to a laboratory value within limit or reference range.

**The LOWEST** value for a patient is defined as the lowest absolute laboratory value during the treatment period. A Lowest value for a cycle is defined as the lowest laboratory value in that cycle.

**The HIGHEST** value for a patient is defined as the highest laboratory value during the treatment period. A highest value for a cycle is defined as the highest laboratory value in that cycle.

**Urinary results**
The category 'Present' corresponds to results '+', '++', '+++' and '++++'. The category 'More than one +' corresponds to results '++', '+++' and '++++'.

**Worst value**
For the urinalysis parameters except specific gravity and pH, the worst class will correspond to 'Presence' class, then 'Trace' and finally 'Absence' will be considered as normal class.
For specific gravity and pH, the worst highest value as well as the worst lowest value will be derived.
For creatinine clearance, the worst class will correspond to "severe" category, then "moderate", then "mild" and finally "normal".

Baseline and post baseline worst grade for High and Low:
- Low: If the result is below lower normal range limit, Low =grade (for gradable parameter), Else Low = 0.
- High: If the result is above upper normal range limit, High =grade (for gradable parameter), Else High = 0.

### 7.4. Vital signs and clinical examination

**Last value under treatment**
For ECOG, weight, BSA, respiratory rate, oxygen saturation, SBP, DBP and HR, the last value under treatment will be derived.

**Change from baseline**
For weight, BSA, respiratory rate, oxygen saturation, SBP, DBP and HR, the change from baseline to to last post-baseline value under treatment will be derived.

**Body Surface Area**
BSA is calculated in the ClinTrial database (by data management department) using the height at inclusion visit and the weight at a corresponding cycle. This derived BSA will be used for compliance/exposure calculations.

The BSA will be calculated using the following Dubois formula (all BSA calculations are rounded to 2 decimal places) (Dubois, 1916).

BSA ($m^2$) = ([Body Weight (kg)] $^{0.425}$ x [Height (cm)] $^{0.725}$) x 0.007184

**ECOG performance status**

**Table (7.4) 1 - Patient Performance Status**

| *GRADE* | *STATUS* |
|---|---|
| | ECOG |
| 0 | Normal unrestricted activity |
| 1 | Arduous physical activity restricted, but patient able to walk unaided and perform light work |
| 2 | Able to walk unaided and independent but unable to work more than half-time |
| 3 | Much less independent. Spends more than half his / her time in bed or seated. |
| 4 | Incapable of looking after him / herself. Completely confined to bed or to a chair |

### 7.5. Electrocardiogram

**Change from baseline to last visit** = Last absolute prolongation - Absolute prolongation at baseline.

## 8. APPENDIX D: QUALITY OF LIFE

Not applicable.

## 9. APPENDIX E: SOFTWARE AND PROGRAMMING CODES

Kaplan Meier survival analysis

```
PROC LIFETEST data= work.data alpha=0.05 method=KM;
        time TIME *CENSOR (censoredval);
strata ARM;
id USUBJID;
RUN;
```

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

## 10. APPENDIX F: EARLY FUTILITY (INTERIM 0)

Not applicable

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

CL3-95026-001 - Statistical Analysis Plan | VV-TMF-130355 | 1.0

# 11. REFERENCES

## Guidelines

Guideline on Missing Data in Confirmatory Clinical Trials – Adopted by CHMP, June 2010, issued as EMA/CPMP/EWP/1776/99 Rev. 1.

ICH E3 - Structure and Content of Clinical Study Reports – Adopted by CPMP, December 1995, issued as CPMP/ICH/137/95/step 5.

ICH E3 Q&A - Structure and Content of Clinical Study Reports - Questions & Answers (R1) - July 2012, issued as EMA/CHMP/ICH/435606/2012.

ICH E9 - Statistical Principles for Clinical Trials - Adopted by CPMP, March 1998, issued as CPMP/ICH/363/96/step 5.

ICH E9(R1) – Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials - Adopted by CHMP, February 2020, issued as EMA/CHMP/ICH/436221/2017.

ICH E14 – The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic drugs – Adopted by CHMP, May 2005, issued as CHMP/ICH/2/04.

CTCAE (Common Terminology Criteria for Adverse Events) version 5.0

## Bibliography

.

Cox DR. Regression Models and Life-Tables Journal of the Royal Statistical Society. Series B (Methodological), 1972;Vol. 34, No. 2:187-220.

Dubois D, Dubois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med. 1916;17:863-871.

.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association 1958;53:457-481.