NOVARTIS

Clinical Development

NIS793

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An open-label, multi-center, phase II platform study evaluating the efficacy and safety of NIS793 and other new investigational drug combinations with standard of care (SOC) anti-cancer therapy for the second line treatment of metastatic colorectal cancer (mCRC)

Statistical Analysis Plan (SAP)

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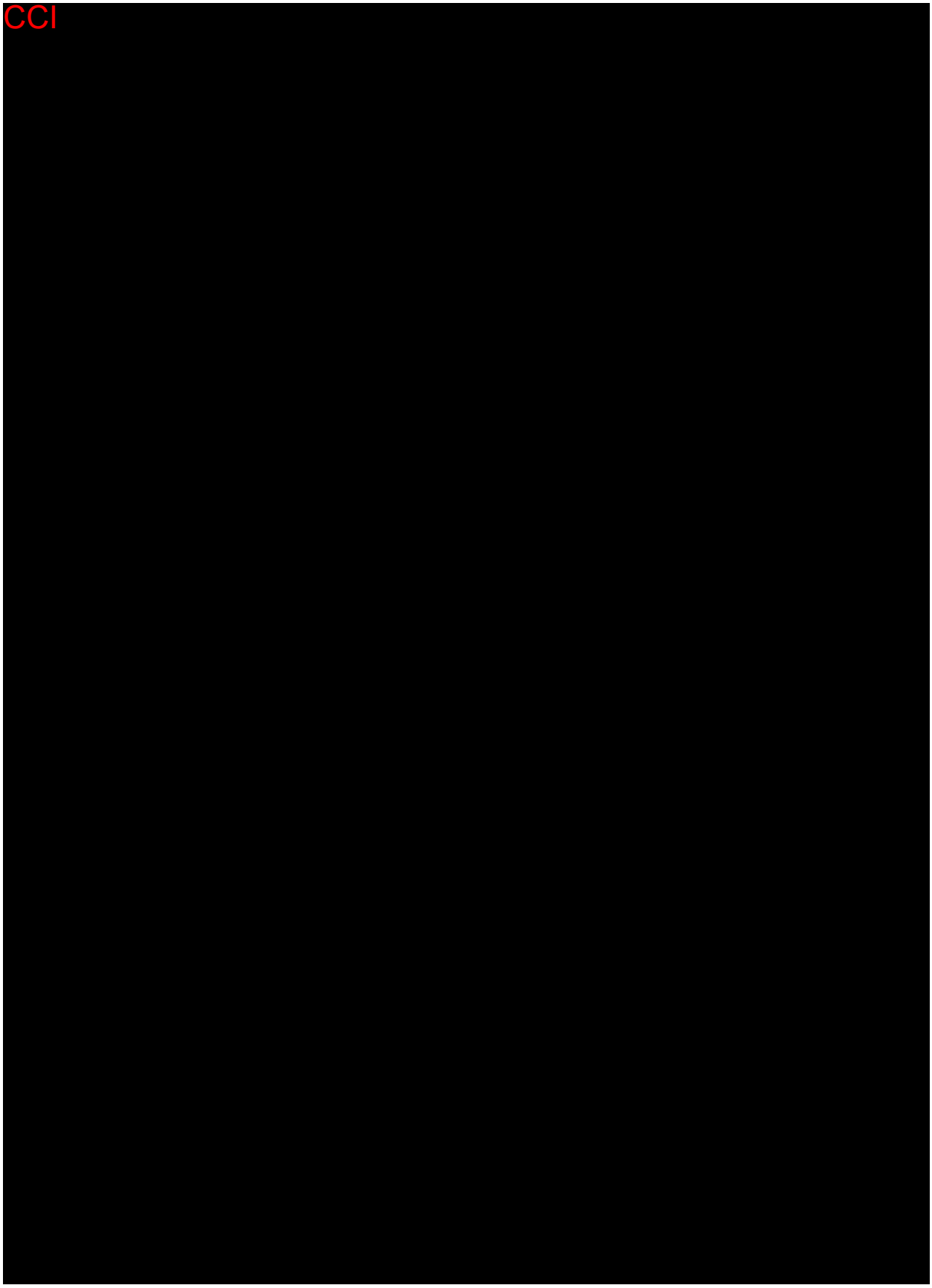
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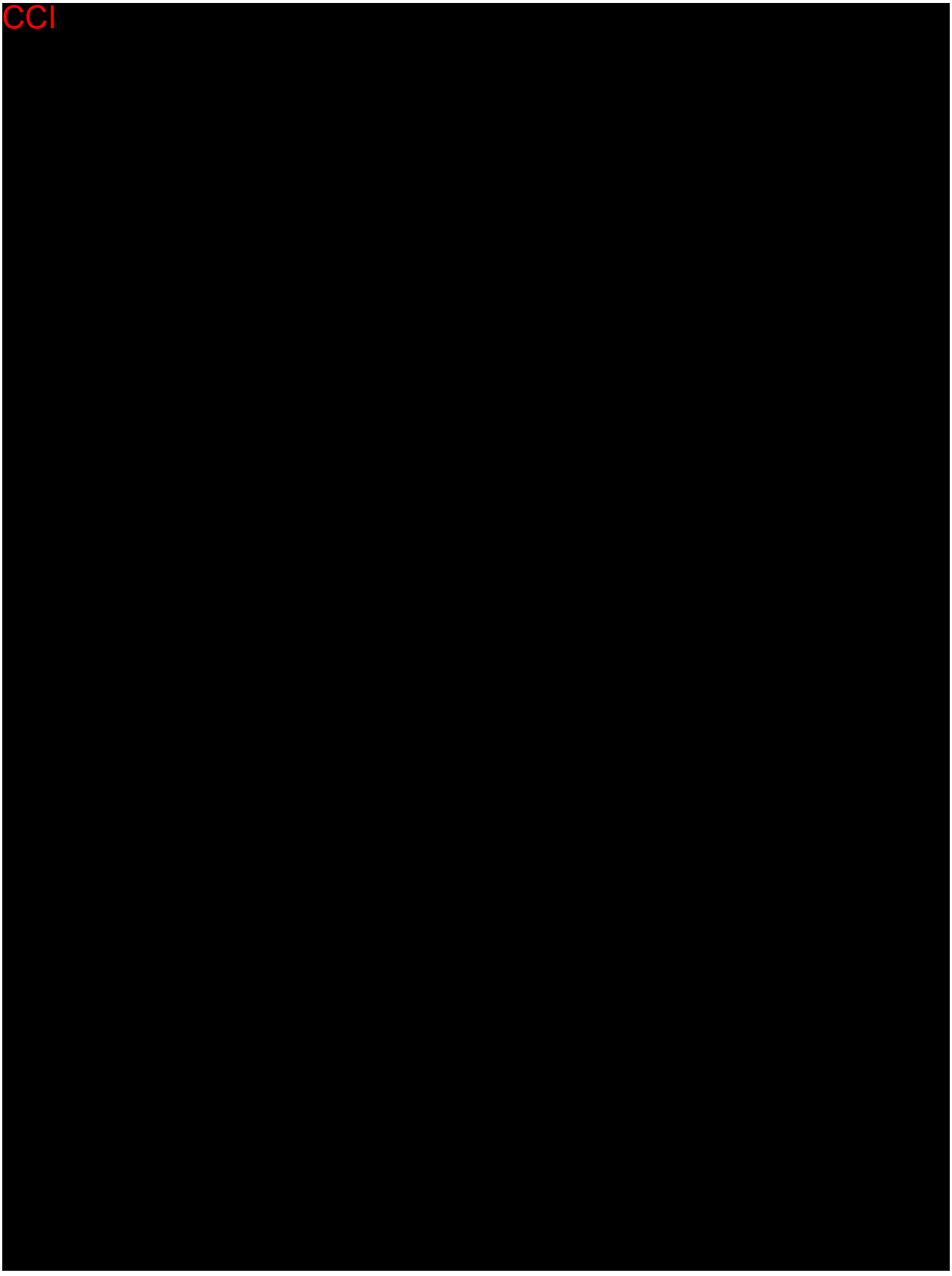
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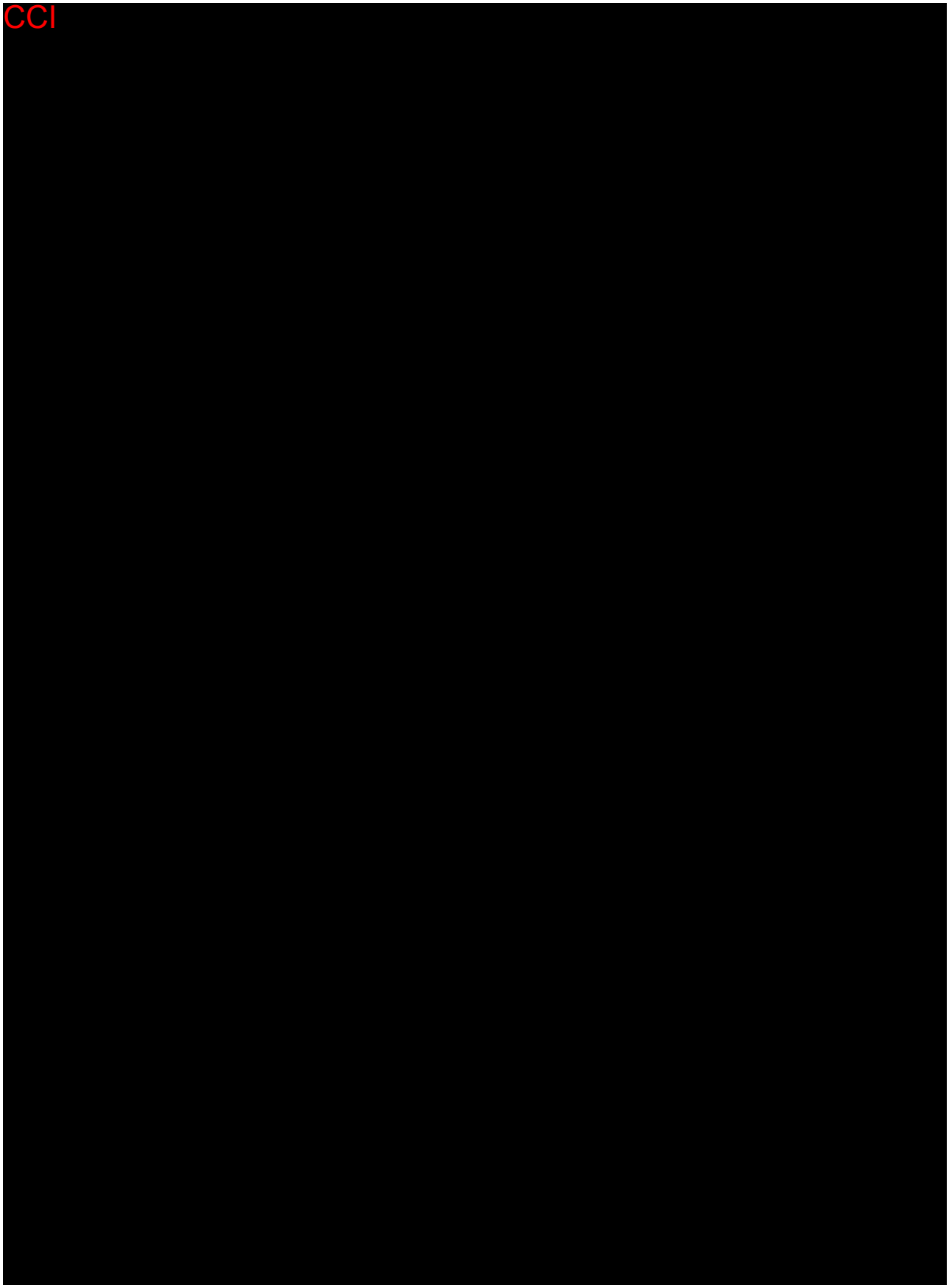
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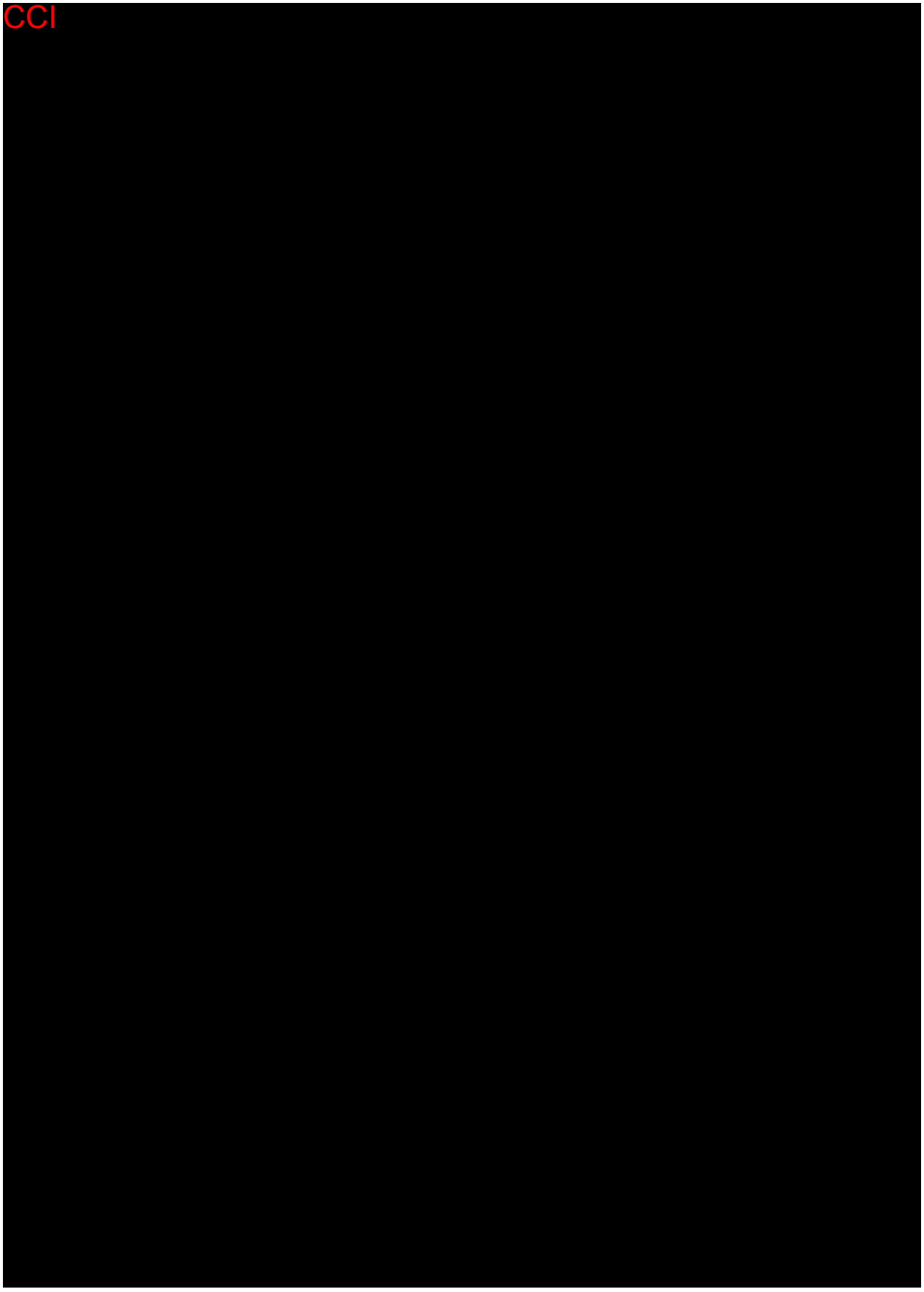
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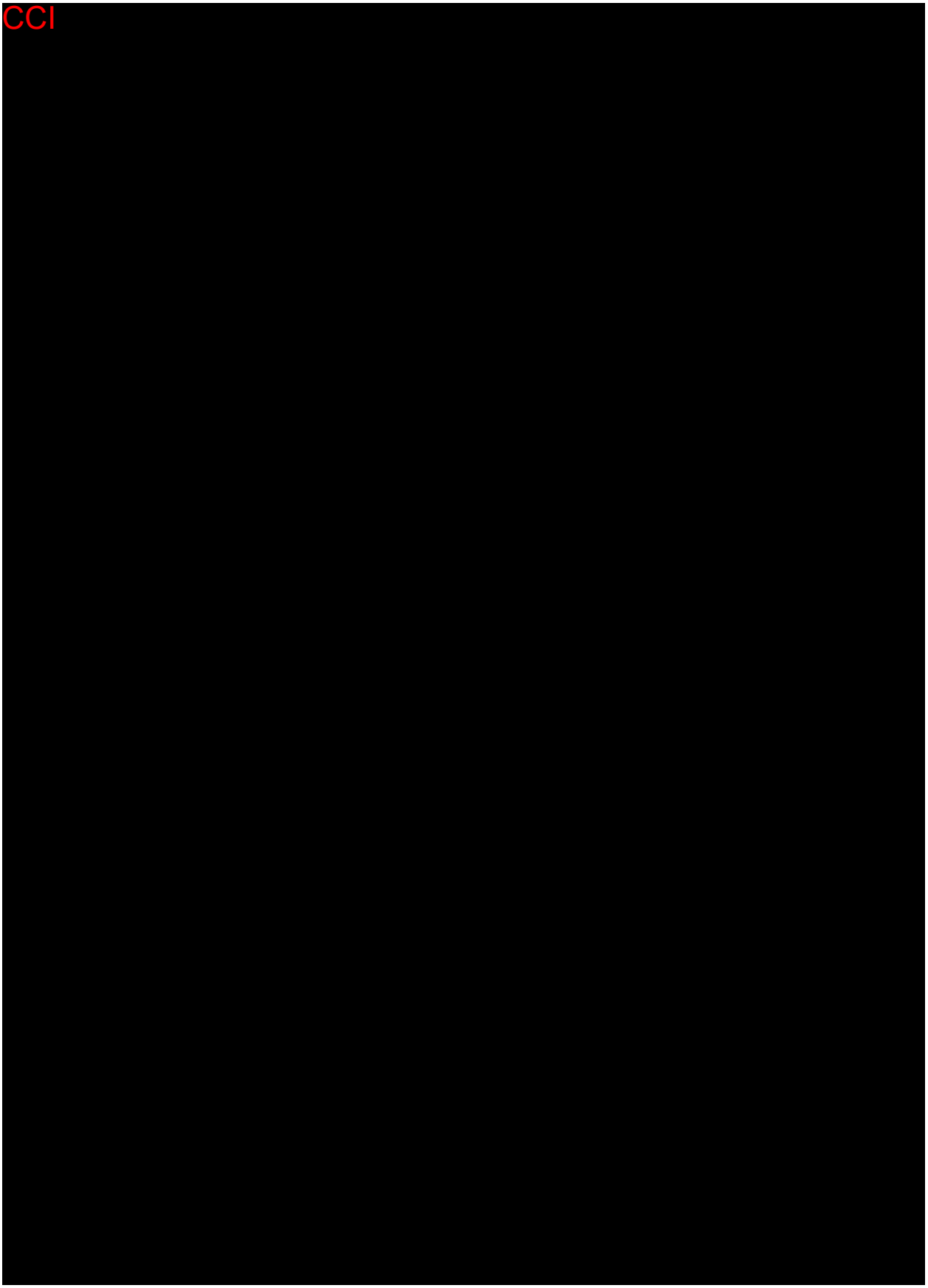


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List of abbreviations

ADA	Anti-drug Antibody
AE	Adverse event
AESI	Adverse Event of Special Interest
ALP	Alanine Phosphatase
ALT	Alkaline Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BOR	Best Overall Response
BSA	Body Surface Area
CD8	Cluster of Differentiation 8
C-FAS	Complete Full Analysis Set
CI	Confidence Interval
mCRC	Metastatic Colorectal Cancer
CR	Complete Response
CSP	Clinical Study Protocol
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DDS	Dose Determining Set
DI	Dose Intensity
DMC	Data Monitoring Committee
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
FAR	First Available Report
FAS	Full Analysis Set
HR	Hazard Ratio
IB	Investigator's Brochure
IG	Immunogenicity
iRECIST	Response Evaluation Criteria in Solid Tumors for Immunotherapy trials
K-M	Kaplan-Meier
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mCRC	metastatic Colorectal Cancer
NMQ	Novartis MedDRA Queries
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set

PD	Pharmacodynamics
PDI	Planned Dose Intensity
PD-L1	Programmed Death-Ligand 1
PDS	Programming Datasets Specifications
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SD	Standard Deviation
SMQ	Standardized MedDRA Queries
SOC	Standard of Care
SOC	System Organ Class
TBL	Total Bilirubin Level
TFLs	Tables, Figures, Listings
TGF-β	Transforming Growth Factor-Beta
TTP	Time-to-Progression
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CNIS793E12201 that will be presented in the final Clinical Study Report (CSR).

The output shells accompanying this document can be found in the Tables, Figures and Listings (TFL) shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document. The content of this SAP is based on protocol amendment v04 dated 11-Mar-2024. All decisions regarding analyses, as defined in the SAP document, have been made prior to database lock of the study data.

All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document without the need to amend.

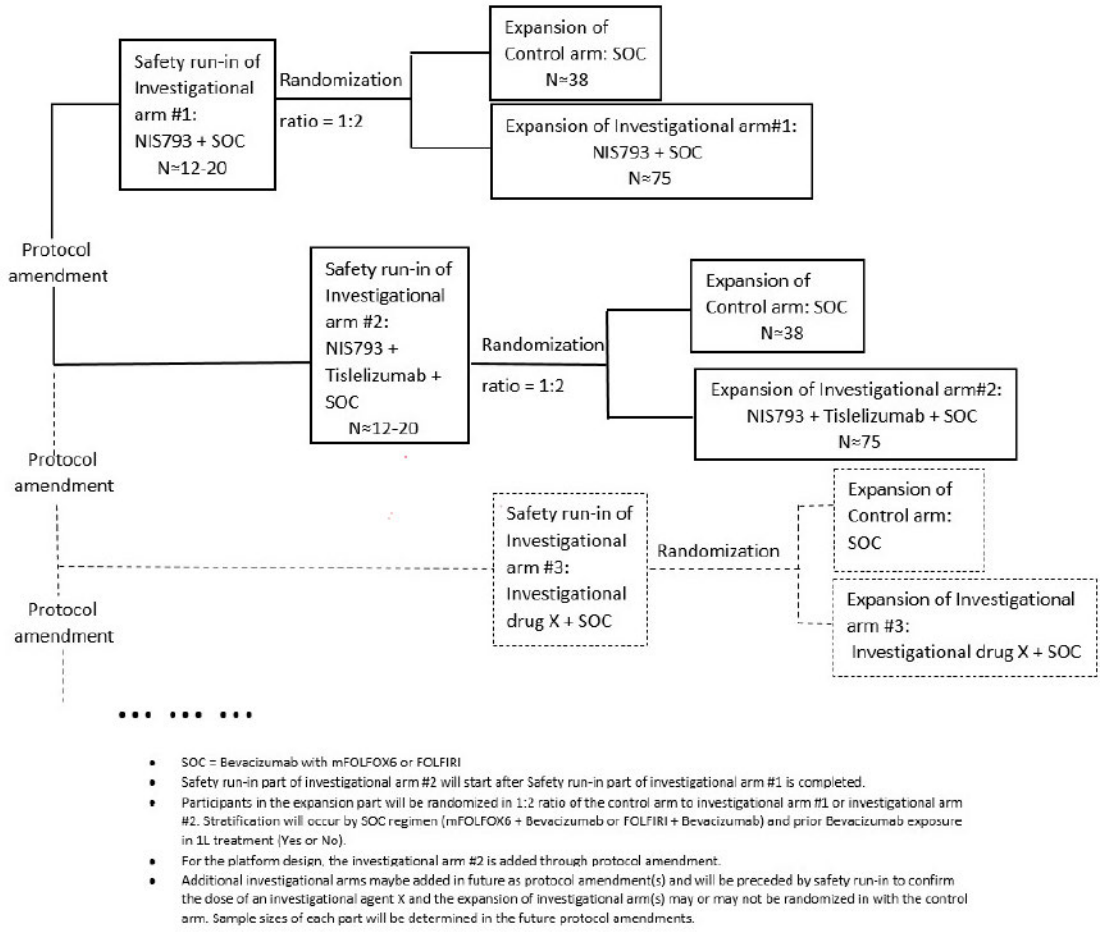
The SAP, TFL shells, and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., IB updates, abstracts, posters, presentations, manuscripts, and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

1.1 Study design

This open-label phase II platform study is to evaluate safety and preliminary efficacy of NIS793 or NIS793+tislelizumab in combination with SOC anti-cancer therapy versus SOC for the second line treatment of mCRC.

The study is expected to enroll up to 20 participants for **Safety run-in** part of each investigational arm and total approximately 225 participants (75 per arm) to the investigational arm #1, investigational arm #2 and control arm for **Expansion part.** An overview of the study design is depicted in Figure 1-1.

Figure 1-1 Overview of Study design

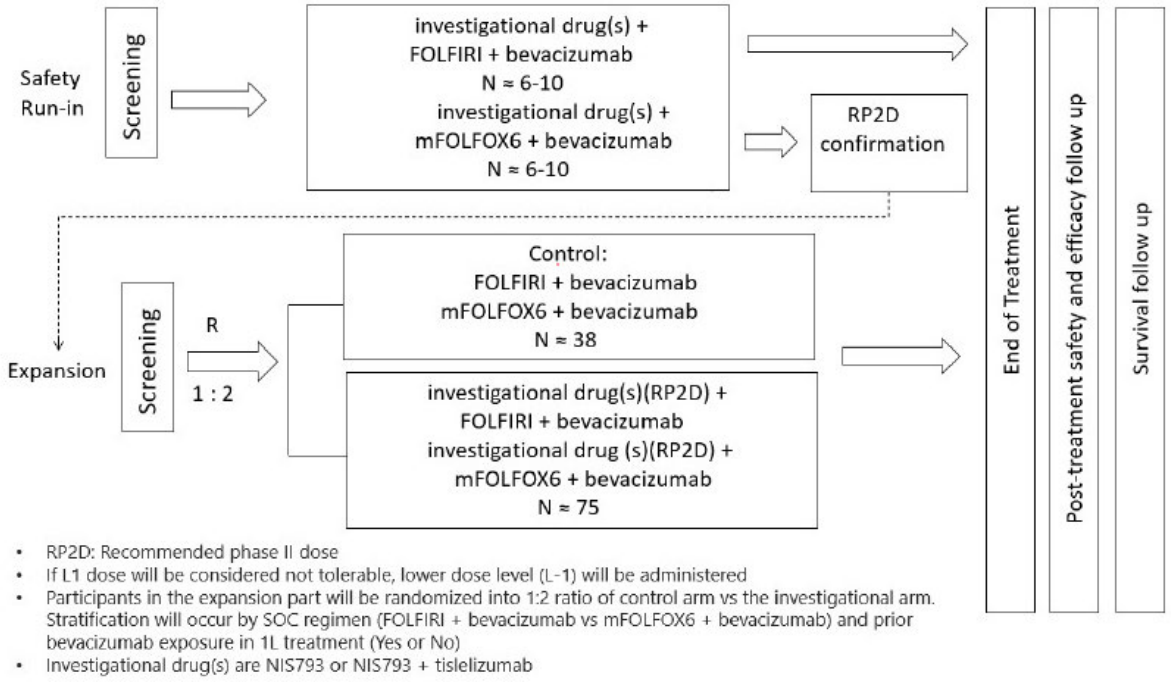


- SOC = Bevacizumab with mFOLFOX6 or FOLFIRI
- Safety run-in part of investigational arm #2 will start after Safety run-in part of investigational arm #1 is completed.
- Participants in the expansion part will be randomized in 1:2 ratio of the control arm to investigational arm #1 or investigational arm #2. Stratification will occur by SOC regimen (mFOLFOX6 + Bevacizumab or FOLFIRI + Bevacizumab) and prior Bevacizumab exposure in 1L treatment (Yes or No).
- For the platform design, the investigational arm #2 is added through protocol amendment.
- Additional investigational arms maybe added in future as protocol amendment(s) and will be preceded by safety run-in to confirm the dose of an investigational agent X and the expansion of investigational arm(s) may or may not be randomized in with the control arm. Sample sizes of each part will be determined in the future protocol amendments.

The study flow of control arm and investigational arm #1 and arm #2 is provided in Figure 1-2.

Stratification will occur by SOC regimen (modified FOLFOX6 +bevacizumab or FOLFIRI + bevacizumab) due to the different safety profiles of the 2 regimens (Tournigand et al 2004) and prior exposure to bevacizumab (yes/no).

Figure 1-2 Study Flow of Control and Investigational arms



- RP2D: Recommended phase II dose
- If L1 dose will be considered not tolerable, lower dose level (L-1) will be administered
- Participants in the expansion part will be randomized into 1:2 ratio of control arm vs the investigational arm. Stratification will occur by SOC regimen (FOLFIRI + bevacizumab vs mFOLFOX6 + bevacizumab) and prior bevacizumab exposure in 1L treatment (Yes or No)
- Investigational drug(s) are NIS793 or NIS793 + tislelizumab

Safety run-in part

The **Safety run-in (SRI) part** will be initiated to confirm RP2D of the investigational drug(s) with SOC anti-cancer therapy. Each **Safety run-in part** will enroll approximately 10 participants for each SOC regimen cohort to achieve at least 6 evaluable participants per cohort based upon protocol defined criteria (approximately 20 participants in total for two SOC regimen cohorts and at least 12 evaluable participants in total for two SOC regimen cohorts). Two SOC regimen cohorts are:

- Investigational drug(s) + modified FOLFOX6 + bevacizumab
- Investigational drug(s) + FOLFIRI + bevacizumab

At each dose level, at least 6 evaluable participants are required to be followed for safety for the full duration of the dose limiting toxicity (DLT) evaluation period. The DLT evaluation period is defined as the first cycle (i.e. 28 days, or 4 weeks) of dosing of study treatment.

If the starting dose (L1) is not considered safe, the dose will be de-escalated to lower dose level-1 (L-1). An additional 10 participants will be enrolled at the lower dose level for that SOC regimen cohort.

RP2D for the investigational drug may be different for the combination with FOLFIRI and mFOLFOX6. The RP2D for each regimen will be established when enrollment and DLT period for the respective regimen is complete, and totality of available safety, PK, and PD data has been analysed, interpreted and reviewed in the safety review meeting.

For Investigational arm #1: SRI arm #1 for FOLFIRI and mFOLFOX were fully enrolled. RP2D for SRI arm #1 FOLFIRI and mFOLFOX were declared , and Expansion arm #1 FOLFIRI and mFOLFOX opened and fully enrolled.

For Investigational Arm #2: SRI arm #2 for FOLFIRI was fully enrolled, RP2D declared and Expansion arm #2 FOLFIRI enrollment was ongoing at the time of study termination. SRI arm #2 for mFOLFOX was fully enrolled CCI [redacted] no data summaries were produced and the BLRM was not updated for for investigational arm #2 mFOLFOX. CCI [redacted] Expansion arm #2 mFOLFOX was never opened for enrollment.Dose confirmation will be guided by a Bayesian logistic regression model (BLRM) based on any DLTs observed for one cycle of treatment (i.e. 28 days, or 4 weeks). The adaptive BLRM will be guided by the Escalation with Overdose Control (EWOC) principle to control the risk of DLT to future patients. The BLRM is a well-established and widely used method to estimate the recommended dose for expansion (RDE) or maximal tolerable dose (MTD) in clinical trials in cancer patients with small sample size. The use of Bayesian response adaptive models for small datasets has been endorsed by academic publications (Babb et al 1998, Neuenschwander et al 2008, Neuenschwander et al 2010, Natanegara et al 2014), and it constitutes an important aspect of the FDA's Critical Path Initiative (FDA 2004).

A safety review meeting, as described in the CSP Section 6.5.2.1, will take place when six evaluable participants have completed 4 weeks of treatment or discontinued earlier due to DLT. The dose decision will be guided by an algorithm specified in CSP Section 6.5.2. If a decision to modify the dosing regimen is made at this time, an additional safety review of a new dosing regimen will take place after six additional evaluable participants have completed 4 weeks of treatment or have discontinued earlier due to DLT.

Expansion part

The decision to open the **Expansion part** of the study will be based on dose confirmation of investigational drug with available safety, relevant PK, and other relevant clinical and laboratory data from the SRI part (Figure 1-2).

Participants in the **Expansion part** will be randomized in 1:2 ratio to the control arm versus investigational arm. Stratification will occur by SOC regimen (modified FOLFOX6 + bevacizumab or FOLFIRI + bevacizumab) due to the different safety profiles of the 2 regimens (Tournigand et al 2004) and prior exposure to bevacizumab (yes/no) (Figure 1-1).

Each arm will enroll approximately 75 participants (total 225 participants for Investigational arm #1, Investigational arm #2 and control arm).

Participants will be treated until unacceptable toxicity, disease progression per RECIST 1.1, withdrawal of consent, or any other condition of treatment discontinuation specified in the protocol, and/or treatment is discontinued at the discretion of the Investigator or the participant .

Treatment beyond PD per RECIST 1.1 is allowed until immune confirmed PD (iCPD) per iRECIST for participants treated in investigational arm #2, under conditions specified in Protocol Section 6.1.4.1. If tislelizumab is discontinued, treatment beyond RECIST 1.1 PD will not be allowed.

Post implementation of protocol amendment 4, treatment beyond PD will no longer be carried out and iRECIST evaluation will no longer be performed since administration of tislelizumab has stopped.

For participants in investigational arm #2 who were permitted to continue study treatment with tislelizumab with or without NIS793 and/or SOC beyond initial disease progression as per RECIST 1.1 according to last version of procotol, they had to continue to follow all study procedures as outlined in Section 8 according to last version of protocol, until the day when tislelizumab permanent discontinued or and until immune confirmed PD (iCPD) per iRECIST, which ever comes earlier. The iRECIST data collected will be listed separately.An independent Data Monitoring Committee (DMC) will monitor safety data during the trial and review efficacy data at interim analysis. A separate DMC SAP will specify the analyses to be performed for the DMC reviews. No formal interim analysis is planned in this study.

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The final analysis will be performed after the completion of the study.

1.2 Study objectives and endpoints

The investigational arm #1 will include NIS793 + SOC anti-cancer therapy.

The investigational arm #2 will include NIS793 + tislelizumab + SOC anti-cancer therapy.

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objectives	**Endpoints for primary objectives**
• **Safety run-in part** To confirm the recommended phase 2 dose (RP2D) of each investigational arm (NIS793 or NIS793+tislelizumab in combination with SOC) (SOC: either modified FOLFOX6 + bevacizumab or FOLFIRI+ bevacizumab chemotherapy regimen)	• **Safety run-in part:** • Incidence of DLTs during the first treatment cycle (4 weeks) of treatment
• **Expansion part:**	• **Expansion part:**

Objectives	Endpoints
To evaluate preliminary efficacy of each investigational arm (NIS793 or NIS793+tislelizumab in combination with SOC anti-cancer therapy) versus control arm(SOC anti-cancer therapy) in terms of progression-free survival (PFS) by Investigator's assessment per RECIST 1.1	• Progression-free survival (PFS) by Investigator's assessment per RECIST 1.1
Secondary objectives	**Endpoints for secondary objectives**
• **Safety run-in part:** To characterize the safety and tolerability of each investigational arm (NIS793 or NIS793+tislelizumab in combination with SOC)	• **Safety run-in part:** • Safety: Incidence and severity of AEs including changes in laboratory parameters, vital signs and ECG parameters • Tolerability: Dose interruptions, reductions and dose intensity
• Preliminary anti-tumor activity of each investigational arm (NIS793 or NIS793+tislelizumab in combination with SOC)	• PFS, overall response rate (ORR), disease control rate (DCR), duration of response (DOR) and time to response (TTR)by Investigator's assessment per RECIST 1.1 and overall survival (OS)
• To characterize the pharmacokinetics (PK) of each investigational treatment (NIS793 or NIS793+tislelizumab in combination with SOC)	• Drug concentrations in serum of each investigational treatment over time and derived PK parameters (e.g. Ctrough, Cmax)
• To characterize the immunogenicity of each investigational treatment (NIS793 or NIS793+tislelizumab in combination with SOC)	• Incidence of antidrug antibodies (ADA), prevalence at baseline and ADA incidence during the treatment for investigational treatment(s).
• **Expansion part:** To evaluate and compare efficacy of each investigational arm and control arm (NIS793 or NIS793+tislelizumab in combination with SOC) in terms of ORR, DCR, DOR, TTR by Investigator's assessment per RECIST 1.1	• **Expansion part:** ORR, DCR, DOR, TTR by investigator's assessment by RECIST 1.1
• To evaluate and compare the overall survival (OS) of each investigational arm and control arm (NIS793 or NIS793+tislelizumab in combination with SOC)	• OS

Objectives	Endpoints
•	
• Safety and tolerability	• Incidence and severity of AEs, changes in laboratory parameters, vital signs and ECG parameters; dose interruptions, reductions and dose intensity
• To characterize the PK of each investigational treatment (NIS793 or NIS793+tislelizumab in combination with SOC)	• Drug concentrations in serum of each investigational treatment over time and derived PK parameters (e.g. Ctrough, Cmax)
• To characterize the immunogenicity of components of each investigational arm(NIS793 or NIS793+tislelizumab in combination with SOC) and control arm	• Incidence of antidrug antibodies (ADA), prevalence at baseline and ADA incidence during the treatment for investigational treatment(s).
Exploratory objectives	**Endpoint(s) for exploratory objectives**
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Objectives	Endpoints
CCI	[redacted]

1.2.1 Primary estimand(s)

The primary estimand is specified for the **Expansion part** only.

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g. premature discontinuation of treatment). Primary estimand is defined only for the **Expansion part**, and the primary scientific question of interest is:

- What is the relative effect of each investigational treatment arm relative to the SOC anti-cancer therapy arm in prolonging PFS by investigator's assessment per RECIST 1.1 in the second line mCRC setting, regardless of study treatment discontinuations or start of a new subsequent antineoplastic therapy or prohibited medication which is not part of assigned study treatment strategy?

The justification for targeting the treatment effects is that we wish to estimate the relative effects of the invstigational treatment strategies in the presence of a) a potentially new anti-cancer therapy that is not a part of the assigned treatment strategy or/and b) in the presence of treatment discontinuation (due to Covid-19 or any reason not related to new anti-cancer therapy).

The primary population is adult participants with MSS mCRC who progressed on or within 6 months after the last dose of one prior line of systemic anti-cancer therapy administered for metastatic disease. Further details about the population are provided in CSP Section 5.

1. **Population**: all participants with MSS mCRC treated with the second line treatment. Further details on the population characteristics are provided in the eligibility criteria.

2. **Treatment**: investigational drug(s) in combination with SOC anti-cancer therapy and SOC alone with or without any new subsequent anti-neoplastic therapy or prohibited medication post randomization/treatment as needed. The SOC anti-cancer therapy will include combination of bevacizumab with either modified FOLFOX6 or FOLFIRI depending on the prior first line treatment used by participants.
3. **Variable**: PFS will be defined as the time from the first date of randomization/treatment to the first documented progression as per RECIST 1.1 per investigator or any-cause death.
4. **Handling of remaining intercurrent events**: (intercurrent event describes how events that may occur after randomization are considered when assessing the treatment effect)
   - Discontinuation of study treatment for any reason: All PFS events will be included in the analysis irrespective of the study treatment discontinuation reasons (treatment policy strategy).
   - Any unforeseen intercurrent events (e.g., Coronavirus Infectious Disease 2019 (COVID-19) pandemic related events): All PFS events will be included in the analysis irrespective of any unforeseen intercurrent events (treatment policy strategy).
5. **Summary measure**: Hazard Ratio for PFS by investigator per RECIST 1.1 between each investigational drug(s) in combination with SOC anti-cancer therapy arm vs SOC anti-cancer treatment arm. After the implementation of protocol amendment 4, there will be no formal hypothesis testing, and HR will be presented as descriptive only.

Stratification factors considered for randomization are: the SOC regimen for treatments (modified FOLFOX6 or FOLFIRI) and the prior exposure to bevacizumab (yes/no).

2 Statistical methods

2.1 Data analysis general information

Novartis will perform the analysis specified in this SAP for the CSR. SAS version 9.4 or later and R version 3.6.1 or later will be used to perform all data analyses and to generate tables, figures, and listings.

2.1.1 Data included in the analysis

Available data from all participants up to the final analysis cut-off date will be analyzed and summarized in this final CSR. An exception is Section 2.13, with an earlier data cut-off and and also the final data-cut off. All events with start date before or on the cut-off date and end date after the cut-off date will be reported as ‘ongoing’. The same rule will be applied to events starting before or on the cut-off date and not having documented end date.

2.1.1.1 Safety run-in Part

After all enrolled patients have completed at least one cycle of treatment (i.e. first 28 days, or 4 weeks) with NIS793 in combination with SOC or NIS793 + tislelizumab in combination with

SOC, lost to follow-up, died, withdrew consent or discontinued the study, the BLRM will be performed to calculate the posterior probabilities of DLT rates in 'underdose', 'targeted toxicity' and 'excessive toxicity' intervals. The dosing regimen may only be used as RP2D for the **Expansion part** if the posterior probability of excessive toxicity (within the interval [0.33, 1]) is less than 25%. All the clinical data by analysis cut-off date including safety data, PK, PD and BLRM inference and results will be thoroughly reviewed by a Safety Review Team (SRT) meeting. The combination dose of NIS793 2100 mg Q2W with SOC or NIS793 2100 mg Q2W + tislelizumab with SOC will be declared as RP2D if the pre-specified conditions are met, see Section 2.5.2 for details.

The reporting and analysis details will be documented in the final CSR. In addition, the analysis of all the safety, PK, efficacy data, etc. generated from the **Safety run-in part** will also be reported in the final CSR.

2.1.1.2 Expansion Part

All primary and secondary objectives will be reported in the CSR at the end of the study.

2.1.1.3 General analysis conventions

Pooling of centers: Unless specified, data from all study centers will be pooled for the analyses. Due to expected small number of participants enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment arm and SOC cohort; a missing category will be included as applicable. Percentages will be calculated using the number of participants in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum)by treatment arm and SOC cohort.

2.1.2 General definitions

Definitions below apply for each study part of the study. A participant included in the **Safety run-in part** will not enter in the **Expansion part**.

2.1.2.1 Investigational drug and investigational treatment

Investigational drug #1 will refer to NIS793.

Investigational drug #2 will refer to NIS793 + tislelizumab.

Standard of care (SOC) treatment will refer to modified FOLFOX6 + bevacizumab or FOLFIRI + bevacizumab.

The terms investigational drug and any drug of SOC treatment may also be referred to as **study drug**.

Investigational treatment #1 will refer to the combination of investigational drug #1 and SOC treatment:

- NIS793 + modified FOLFOX6 + bevacizumab or
- NIS793 + FOLFIRI + bevacizumab

Investigational treatment #2 will refer to the combination of investigational drug #2 and SOC treatment:

- NIS793 + tislelizumab + modified FOLFOX6 + bevacizumab or
- NIS793 + tislelizumab + FOLFIRI + bevacizumab

The terms investigational treatment and SOC treatment may also be referred to as **study treatment**.

2.1.2.2 Date of first administration of study drug

The date of first administration of study drug is defined as the first date when a non-zero dose of study drug is administered and recorded on the treatment page eCRF.

2.1.2.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug is administered and recorded on the treatment page eCRF.

2.1.2.4 Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of study treatment was administered as per treatment page eCRF. The date of first administration of study treatment will also be referred as ***start of study treatment***.

For example, if the first dose of NIS793 is taken on 15OCT2021, and first dose of modified FOLFOX6 + bevacizumab or FOLFIRI + bevacizumab is taken on 18OCT2021, then the date of first administration of study treatment is on 15OCT2021.

2.1.2.5 Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment was administered as per treatment page eCRF. The date of last administration of study treatment will also be referred as ***end of study treatment***.

For example, if the last dose of NIS793 has been taken on 15FEB2022, and the last dose of modified FOLFOX6 + bevacizumab or FOLFIRI + bevacizumab is taken on 18FEB2022, then the date of last administration of study treatment is 18FEB2022.

2.1.2.6 Study day

The study day describes the day of the event or assessment date, relative to the reference start date. The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if the event is on or after the reference start date;

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if the event precedes the reference start date.

In the **Safety run-in part**, the reference start date for all assessments is the start date of study treatment administration. In the **Expansion part**, the reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose adjustments, etc.) is the start date of study treatment administration. The reference start date for all other non-safety assessments (i.e. tumor assessment, survival time, disease progression, tumor response, and ECOG performance status) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

2.1.2.7 Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

2.1.2.8 Baseline

In the **Safety run-in part,** the last available assessment on or before the date of start of study treatment will be defined as "baseline" assessment for both safety and efficacy evaluation.

In the **Expansion part**, for efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization will be defined as "baseline" value or "baseline" assessment.

In the context of baseline definition, the efficacy evaluations also include biomarkers and ECOG performance status. For safety evaluations, the last available assessment on or before the date of start of study treatment is defined as ''baseline" assessment. For safety parameters (e.g. ECGs or vital signs), where the study requires multiple replicates per timepoint, the average of these measurements would be calculated for baseline (if not already available in the database).

If participants have no value as defined above, the baseline value will be defined as missing.

2.1.2.9 On-treatment assessment/event and observation periods

For adverse event reporting, the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period:*** from day of participant's informed consent to the day before first administration of study treatment;
2. ***on-treatment period***: from date of first administration of study treatment up to 30 days after date of last actual administration of any study treatment (including start and stop date);
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

An ***on-treatment assessment*** is defined as any assessment performed after the date of first administration of any study drug i.e. assessments performed in the following time interval

(including the lower and upper limits): from date of first administration of any study drug +1 up to 30 days after the date of last administration of study treatment.

An ***on-treatment adverse event*** (or ***treatment-emergent*** AEs) is defined as any adverse event reported in the on-treatment period.

Safety summaries (tables, figures) and summaries of on-treatment deaths include only data from the on-treatment period with the exception of baseline data, which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, all deaths which occurred during the study (i.e. during the on-treatment and post-treatment periods) will be summarized.

In protocol amendment 4, the safety follow-up period has been reduced from 120 days to 30 days following the last dose of study treatment. However, there should be subjects who had their safety follow-up period according to the last version of protocol. Thus, additional listings will be displayed to all AE, AE related to study treatment, all SAE, as well as new antineoplastic therapies collected up to 120 days after last administration of NIS793 or tislelizumab.

In addition, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

2.1.2.10 Window for multiple assessments

In order to summarize ECOG performance status, and other assessments data collected by visits, the time window of each assessment needs to be defined. The following general rule will be applied in creating the assessment windows: If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used.

Table 2-1 Time windows for ECOG performance status and other assessments

ee

For ECOG PS

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (screening)	Before study Day 1	< Day 1
Cycle 1 Day 1	Study Day 1*	Study Day 1
Cycle 1 Day 15	Study Day 15	Study Day 8-21
Cycle 2 Day 1	Study Day 29	Study Day 22-36
Cycle 2 Day 15	Study Day 43	Study Day 37-51
Cycle 3 Day 1	Study Day 57	Study Day 52-70
.....		
Cycle k Day 1	Study Day d = (k - 1) * 28 + 1	Study Day (k - 1) * 28-13 to (k - 1) * 28+14
EOT	EOT date	Study Day EOT – 7 days to EOT + 14 days
Safety follow-up	EOT date + 30 days	EOT date + 15 days to EOT

		date + 30 days
*Study Day 1 = First study treatment		
For Immunogenicity:		
C1D1	Study Day 1	≤ Study Day 1
C1D15	Study Day 15	Study Day 8-22
C3D1	Study Day 57	Study Days 50 to 65
C3D15	Study Day 71	Study Days 64 to 78
C6D1	Study Day 141	Study Days 127 to 154
.....		
Cycle k Day 1 (with k = 12,18, 24)	Study Day 28*(k-1)+1	Study Day 28*(k-1)-13 to 28*(k-1)+14
EOT	EOT date	Study Day EOT – 7 days to EOT + 14 days
Safety follow-up1	EOT date + 60 days	EOT date + 55 days to EOT date + 75 days
Safety follow-up2	EOT date + 90 days	EOT date + 76 days to EOT date + 90 days

2.1.2.11 Last contact date

The last contact date will be derived for participants not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-2 Last contact date data sources

Source data	Conditions
Date of Randomization	No condition
Last date participant was known to be alive from Survival Follow-up page	Participant status is reported to be alive
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End* dates from treatment page	Non-missing dose. Doses of 0 are allowed
End of treatment date from end of treatment page	No condition
Imaging assessment date	Imaging marked as done
Laboratory/PK collection dates	Sample collection marked as ‘done’
Vital signs date	At least one non-missing parameter value

Source data	Conditions
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the participant was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a treatment page) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring, if coming from 'Survival information' eCRF.

The last contact date will be used for censoring of participants in the analysis of overall survival endpoints.

2.2 Analysis sets

2.2.1 Analysis Set Definition

A participant is considered to be enrolled into the study if they have signed the main study informed consent. Only participant who have signed main study informed consent will be included in the analysis data sets.

2.2.1.1 Study Part information (Safety run-in part or Expansion Part) will be collected from Study Part page of the CRF.Full Analysis Set

Safety run-in Part

For the **Safety run-in part**, the Full Analysis Set (FAS) comprises all participants that received any study drug. Participants will be analyzed according to the treatment(s) received (NIS793+ modified FOLFOX6/FOLFIRI + bevacizumab, NIS793+tislelizumab modified FOLFOX6/FOLFIRI + bevacizumab), where treatment received is defined as:

- the treatment assigned if the participant received at least once (i.e. at least one dose of NIS793 or tislelizumab as appropriate), or
- the first treatment received if the assigned treatment was never received.

The terms **study drug** above refer to investigational drug and any drug of SOC treatment.

If there is any subject who has been assigned to **Safety run-in part**, but never take any dose of NIS793 or Tislelizumab, this subject will still be included in the Full Analysis Set of Safety run-in part. A brief description of such subject will be provided.

If there is any subject who has been assigned to **Safety run-in part**, but never take any dose of **study drug**, this subject will not be included in the Full Analysis Set of Safety run-in part.

Expansion Part

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned by randomization or treatment received (if not randomized). According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

2.2.1.2 Safety Set

All safety endpoints will be analyzed based on the safety sets.

The two regimens modified FOLFOX6 and FOLFIRI will be analyzed separately.

Safety run-in part

The Safety set includes all participants who received at least one dose of study treatment (i.e. at least one dose of any drug of the study treatment (including incomplete infusion)). Participants in the **Safety run-in part** will be analyzed according to treatment received (NIS793+ modified FOLFOX6/FOLFIRI + bevacizumab, NIS793+tislelizumab modified FOLFOX6/FOLFIRI + bevacizumab), where treatment received is defined as:

- the treatment assigned if the participant received at least once (i.e. at least one dose of NIS793 or tislelizumab as appropriate), or
- the first treatment received if the assigned treatment was never received.

If there is any subject who has been assigned to Safety run-in part, but never take any dose of NIS793 or Tislelizumab, this subject will still be included in the Safety Set of Safety run-in part. A brief description of such subject will be provided.

If there is any subject who has been assigned to Safety run-in part, but never take any dose of study drug, this subject will not be included in the Safety Set of Safety run-in part.

Expansion part

The Safety set includes all participants who received at least one dose of study treatment (i.e. at least one dose of any drug of the study treatment (including incomplete infusion)). Participants in the **Expansion part** will be analyzed according to treatment received (NIS793+ modified FOLFOX6/FOLFIRI + bevacizumab or modified FOLFOX6/FOLFIRI + bevacizumab, NIS793+tislelizumab modified FOLFOX6/FOLFIRI + bevacizumab or modified FOLFOX6/FOLFIRI + bevacizumab), where treatment received is defined as:

- the randomized treatment assigned if the participant received at least once (i.e. at least one dose of NIS793 or tislelizumab as appropriate), or
- the first treatment received if the randomized treatment was never received.

In particular, for patients randomized to NIS793+SOC, the treatment received will be NIS793+SOC if the patient has received at least one dose of NIS793. If a patient randomized to NIS793+ SOC, but never received any NIS793, he/she will be will be contribute to the Safety Set of SOC arm. For patients randomized to NIS793+tislelizumab+SOC, the treatment received will be NIS793+tislelizumab+SOC if the patient has received at least one dose of NIS793 and at least one dose of tislelizumab; if a patient randomized to NIS793+tislelizumab+SOC, received NIS but never received any tislelizumab, he/she will be contribute to the Safety Set of

NIS793+SOC; if a patient randomized to NIS793+tislelizumab+SOC, but never received any NIS793 or tislelizumab, he/she will be will be contribute to the Safety Set of SOC arm. Similarly, for patients randomized to SOC the treatment received will be SOC if the patient has received at least one dose of SOC without concomitant NIS793 or tislelizumab.

2.2.1.3 Dose-Determining Set

Safety run-In part

The Dose Determining Set (DDS) consists of all participants in the **Safety run-in part of each investigational arm** who met the minimum exposure criterion and have sufficient safety evaluations after 1 cycle (i.e., 4 weeks) of treatment or experienced a DLT during the first cycle of treatment, i.e. the first cycle (28 days or 4 weeks) of dosing.

For investigational arm #1 NIS793+SOC, the minimum exposure criterion is planned doses of NIS793 (2 dosing for Q2W, or 1 dosing for Q4W) and at least 1 dosing for SOC anti-cancer therapy within the first treatment cycle (i.e. 4 weeks) of study treatment.

For investigational arm #2 NIS793+tislelizumab+SOC, the minimum exposure criterion is the planned doses of NIS793 (2 dosing for Q2W or 1 dosing for Q4W), the planned dose of tislelizumab (1 dosing for tislelizumab), and at least 1 dosing for SOC anti-cancer therapy within the first treatment cycle (i.e., 4 weeks) of study treatment. If the participant did not receive the planned dosages due to DLT, the participant will be considered as meeting the minimum exposure criterion.

The planned dosage for NIS793 is 2100 mg Q2W or 2100 mg Q4W (only applicable in case of a lower dose arm in **Safety run-in part**). The planned dosage for tislelizumab is 300 mg Q4W. The planned dosage for FOLFIRI or modified FOLFOX6 + bevacizumab are shown below:

- FOLFIRI + bevacizumab is administered on days 1 and 15 of each 28-day cycle:
  - 5-Fluorouracil 400 mg/m^2 i.v. bolus followed by 2400 mg/m^2 as a 46-h continuous infusion
  - Leucovorin (folinic acid) 400 mg/m^2 i.v. (or levoleucovorin 200 mg/m^2 i.v., where substitution is permissible per local regulations)
  - Irinotecan 180 mg/m^2 i.v.
  - Bevacizumab 5 mg/kg
- Modified FOLFOX6 + bevacizumab is administered on days 1 and 15 of each 28-day cycle:
  - 5-Fluorouracil 400 mg/m^2 i.v. bolus followed by 2400 mg/m^2 as a 46-h continuous infusion
  - Leucovorin (folinic acid) 400 mg/m^2 i.v. (or levoleucovorin 200 mg/m^2 i.v., where substitution is permissible per local regulations)
  - Oxaliplatin 85 mg/m^2 i.v.
  - Bevacizumab 5 mg/kg

Participants who do not experience a DLT during the first 4 weeks of treatment are considered to have sufficient safety evaluations if they have been observed for 4 weeks following the first

dose and are considered by the Safety Review Team (SRT) to have sufficient safety data in the CRF and source document to conclude that a DLT did not occur. SRT will consist of Novartis personnel and the investigators whose sites have enrolled participants in the **Safety run-in part**. Additionally, members of the DMC will be invited to join the SRT as observers.

2.2.1.4 Pharmacokinetic Analysis Set

Safety run-in part and Expansion part

Individual Pharmacokinetic analysis sets (PAS) will be defined for NIS793 (NIS-PAS) and tislelizumab (TSL-PAS). Each of the PAS includes all participants who provide an evaluable PK profile for this specific PAS. A profile is considered to be evaluable if **all** of the following conditions are satisfied:

- Participant receives at least one dose (complete infusion) of the planned treatments
- Participant provides at least one valid concentration
- For pre-dose samples, have the sample collected before the next dose administration

Participants may be removed from PK analysis on an individual basis depending on the number of available blood samples. These participants will be identified and justified at the time of analysis.

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2.2.1.5 Immunogenicity Analysis Set

Safety run-in part and Expansion part The immunogenicity (IG) sets for NIS793 and tislelizumab includes two parts: IG prevalence set and IG incidence set:

- The IG prevalence set includes all participants in the FAS with a determinant baseline IG sample or at least one determinant post-baseline IG sample.
- The IG incidence set includes all participants in the IG prevalence set with a determinant baseline IG sample and at least one determinant post-baseline IG sample.

The definition of a determinant sample is detailed in Section 2.10.1.

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Participant Classification

Participants may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific participant classification rules defined in Table 2-3.

Table 2-3 Participant classification based on protocol deviations and non-protocol deviation criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written informed consent	**Safety run-in part**: No dose of any component of study treatment

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
		Expansion part: Not applicable
Safety Set	No written informed consent	No dose of any component of study treatment
DDS	No written informed consent	See definition of DDS
NIS-PAS, TSL-PAS	No written informed consent	See definitions of NIS-PAS and TSL-PAS
Immunogenicity prevalence set	No written informed consent	Participants without a determinant baseline IG sample or at least one determinant post-baseline IG sample
Immunogenicity incidence set	No written informed consent	Participants without a determinant baseline IG sample and at least one determinant post-baseline IG sample

Withdrawal of inform consent

Any data collected in the clinical database after a participant withdraws informed consent from all further participation in the trial will not be included in the analysis. The date on which a participant withdraws full consent is recorded in the eCRF.

Additional data, for which there is a separate informed consent, collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.2 Subgroup of interest

Post implementation of protocol amendment 4, no subgroup analyses will be performed.

2.3 Participant disposition, demographics and other baseline characteristics

Summaries and listings described in this section will be based on the FAS, separately for participants in the **Safety run-in part** and in the **Expansion part**. Summaries will be reported by treatment arms, and stratified by thetwo SOC regimen:

- Investigational drug(s) + modified FOLFOX6 + bevacizumab
- Investigational drug(s) + FOLFIRI + bevacizumab

No inferential statistics will be provided.

2.3.1 Participant disposition

The number (%) of treated (randomized) participants will be presented for the **Safety run-in part** (**Expansion part**). The number (%) of participants who are still on treatment, who

discontinued the study phases, and the reason for discontinuation will be presented. Screen failure participants will be reported in a listing with the reasons for not starting the study treatment, but will not be included in any analyses.

2.3.2 Demographic and baseline data

Demographic and other baseline data including disease characteristics will be summarized descriptively for participants in the **Safety run-in part** using the Safety Set and by treatment arm for participants in the **Expansion part** using the FAS. Categorical data (e.g. gender, age groups: <65 years vs ≥65 years, ECOG performace, previous therapy of bevacizumab: yes vs no, sideness of colon (left vs right) or transverse) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index (BMI)) will be summarized by descriptive statistics (e.g. N, mean, median, and standard deviation, percentiles, minimum and maximum). BMI (kg/m^2) will be calculated as weight[kg] / (height[m]^2) using weight and height at Baseline.

2.3.3 Medical history

Medical history and current medical conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT), using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting. The MedDRA version will be specified in the CSR as a footnote in the applicable tables/listings.

2.3.4 Diagnosis and extent of cancer

The summaryof diagnosis and extent of cancer (disease history) will include primary site of cancer, details of tumor histology/cytology, histologic grade, stage at initial diagnosis with time since initial diagnosis, stage at time of study entry, number and type of metastatic sites. Metastatic sites will be based on diagnosis page.

Imputation rules for partially missing dates are provided in Section 5.1.

2.3.5 Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the edit-check specification) overall and by treatment arm. Protocol deviations leading to exclusion from analysis sets and protocol deviations due to COVID-19 will be tabulated separately overall and by treatment arm as specified in Section 2.2. All protocol deviations will be listed.

2.3.6 Analysis sets

The number (%) of participants in each analysis set (defined in Section 2.2) will be summarized and listed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Randomized part

2.4.1.1 Study treatment / compliance

Cumulative dose, dose intensity (DI), and relative dose intensity (RDI) will be summarized separately for each component of study treatment by treatment arms. Duration of exposure will be calculated for each component of study treatment by treatment arms. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of participants in each interval. Details of the derivations and summaries are provided in the following sections.

Participant level listings of all doses administered on treatment along with dose change reasons will be produced.

Safety sets will be used for all summaries and listings of study treatment.

For the missing date of last administration, use the data handling rule in Section 5.1.4.

For the preparation of DSUR/PSUR updates for Tislelizumab, number of subjects exposed to Tislelizumab by sex, age and race on the Safety Set will be summarized.

2.4.1.1.1 Duration of study treatment exposure

Duration of study treatment exposure is defined considering the duration of exposure of each study drug as:

Duration of exposure to study treatment (days) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

Summary of duration of exposure of study treatment will be categorized into time intervals (<1 month, at least 1 month, at least 3 months 3, at least 6 months, at least 12 months, at least 18 months, at least 24 months). and continuous summaries (i.e. mean, standard deviation etc) using months as time units.

Note: If the last record in DAR CRF is a zero dose, this record will not be used in the analyses. For participants who have ongoing treatment, see Section 5.1.4.

Duration of study drug exposure (for NIS793, tislelizumab, FOLFIRI/modified FOLFOX and bevacizumab) is defined according to dosing regimen for each study drug as outlined in Section 2.1.2.

Duration of exposure (days) = (last date of exposure to study drug) – (date of first administration of study drug) + 1

Table 2-4 Definition of last date of exposure to study drug

Scenario	Definition of last date of exposure to study drug	Example

NIS793: Study drug with a Q2W/Q4W (lower dose level) regimen	The planned end date of the last cycle in which the last non-zero dose of the study drug was last administered.	In a 28 day cycle with a Q2W/Q4W regimen, the last date of exposure is the date of any infusion in the last cycle + 13 days for Q2W/ +27 for Q4W.
Tislelizumab: Study drug with a Q4W regimen	The planned end date of the last cycle in which the last non-zero dose of the study drug was last administered.	In a 28 day cycle with a Q4W regimen, the last date of exposure is the date of any infusion in the last cycle +27.
FOLFIRI + bevacizumab / Modified FOLFOX6 + bevacizumab: Study drug with a Day 1 and 15 regimen	The planned end date of the last cycle in which the last non-zero dose of the study drug was last administered.	In a 28 day cycle with a Day 1, and 15 regimen, the last date of exposure is the date of infusion in the last cycle + 13 days.
Note: If the participant died or was lost to follow-up before the derived last date, the last date of exposure to study drug is the date of death or the date of last contact, respectively. If the derived last date of exposure goes beyond the data cut-off date, it should be truncated to the date of data cut-off.		

2.4.1.1.2 Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized using descriptive statistics by treatment arm for each of the study treatment components, respectively. For participants who do not receive any drug the cumulative dose will be set to zero. The cumulative dose is calculated from the DAR eCRF.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the participant is on the study treatment as documented in the treatment page eCRF.

For participants who did not take any drug, the actual cumulative dose is by definition equal to zero for that drug.

For intermittent dosing, the actual cumulative dose should be defined based on the days when the participant is assumed to have taken a non-zero dose during dosing periods.

NIS793

For NIS793 the planned cumulative dose is the planned starting dose summed over the number of expected infusions during the treatment.

Tislelizumab

For tislelizumab the planned cumulative dose is the planned starting dose summed over the number of expected infusions during the treatment.

FOLFIRI + bevacizumab / Modified FOLFOX6 + bevacizumab

For FOLFIRI/Modified FOLFOX6 the dose in mg/m2 at cycle N is equal to the dose administered (mg) at cycle N divided by the body surface area (BSA) at the beginning of cycle N using the weight measured before the infusion. For FOLFIRI/Modified FOLFOX6, the dose in mg/m^2 at cycle N will be the sum of the 2 doses planned to be received at Days 1 and 15 of cycle N. The dose in mg/m^2 will be calculated using the BSA at the beginning of the cycle (i.e. Day 1).

BSA (m^2) at cycle N = $\sqrt{Wt\ (kg) * Ht(cm)/3600}$ (Mosteller formula),

where Wt=weight at the beginning of cycle N (usually this is the weight taken before the infusion of cycle N or last weight available if this is missing) and Ht=Height at the beginning of the study. For Bevacizumab the dose in mg/kg at cycle N is equal to the dose administered (mg) at cycle N divided by the body weight at the beginning of cycle N using the weight measured before the infusion. The dose in mg/kg at cycle N will be the sum of the 2 doses planned to be received at Days 1 and 15 of cycle N.

2.4.1.1.3 Dose intensity and relative dose intensity

The dose intensity (DI) and the relative dose intensity (RDI) for each study treatment (NIS793 and every component of SOC regimen) will be summarized by descriptive statistics. In addition, categorical summary of RDI for each study treatment will be presented.

- **Planned dose intensity** (PDI) per cycle is defined as the protocol planned total dose for a 28-day cycle for each study treatment.

For example:

For NIS793 2100 mg Q2W, PDI is 2100*2 = 4200 mg/cycle.

For NIS793 2100 mg Q4W, PDI is 2100 mg/cycle.

For tislelizumab 300 mg Q4W, PDI is 300 mg/cycle.

For FOLFIRI + bevacizumab:

- 5-Fluorouracil 400 mg/m^2 i.v. bolus followed by 2400 mg/m^2 as a 46-h continuous infusion: PDI is 2400*2 + 400*2=5600 mg/m^2 /cycle
- Leucovorin (folinic acid) 400 mg/m^2 i.v. (or levoleucovorin 200 mg/m^2 i.v., where substitution is permissible per local regulations): PDI is 400*2=800 mg/m^2 /cycle for Leucovorin (or PDI 200*2=400 mg/m^2 /cycle for levoleucovorin)
- Irinotecan 180 mg/m^2 i.v.: PDI is 180*2=360 mg/m^2 /cycle
- Bevacizumab 5 mg/kg: PDI is 5*2=10 mg/kg/cycle

For Modified FOLFOX6 + bevacizumab:

- 5-Fluorouracil 400 mg/m^2 i.v. bolus followed by 2400 mg/m^2 as a 46-h continuous infusion: PDI is 2400*2 + 400*2 = 5600 mg/m^2 /cycle

- Leucovorin (folinic acid) 400 mg/m^2 i.v. (or levoleucovorin 200 mg/m^2 i.v., where substitution is permissible per local regulations): PDI is 400*2=800 mg/m^2 /cycle for Leucovorin (or PDI 200*2=400 mg/m^2 /cycle for levoleucovorin)
- Oxaliplatin 85 mg/m^2 i.v., PDI is 85*2=170 mg/m^2 /cycle
- Bevacizumab 5 mg/kg, PDI is 5*2=10 mg/kg/cycle

- **Dose intensity** (DI) for patients with non-zero duration of exposure is defined as follows:
  DI =(actual cumulative dose) / (number of cycles on treatment)

For NIS793 Q2W:

Number of cycles on treatment=[(last date of administration of NIS793) – (first date of administration of NIS793) + 14]/28

For NIS793 Q4W:

Number of cycles on treatment=[(last date of administration of NIS793) – (first date of administration of NIS793) + 28]/28

For tislelizumab Q4W:

Number of cycles on treatment=[(last date of administration of tislelizumab) – (first date of administration of tislelizumab) + 28]/28

For SOC regimen:

For components of FOLFIRI or Modified FOLFOX6:

DI (mg/m^2/cycle) = {Actual cumulative dose (mg) / BSA (m^2) / [(last date of administration of study drug - first date of administration of study drug + 14)]}/28

For Bevacizumab:

DI (mg/kg/cycle) = {Actual cumulative dose (mg) / Weight (kg) / [(last date of administration of study drug - first date of administration of study drug + 14)]}/28

- **Relative dose intensity** (RDI) is defined as follows:

RDI = DI (dose unit/cycle) / PDI (dose unit/cycle), for NIS793, tislelizumab and every components of SoC.

The DI, PDI and the RDI will be summarized for each study drug component by descriptive statistics by treatment arm. RDI will be summarized in percentage. Categorical summaries and the continuous summaries of RDI (i.e. mean, standard deviation etc.) will be presented.

2.4.1.1.4 Dose changes, interruptions, or permanent discontinuations

The number of participants who have dose changes, dose interruptions and permanent discontinuations and corresponding reasons, will be summarized by treatment arms, for each of the study drug components. All dosing data will be listed.

'Type of change' and 'Dose permanently discontinued' fields from the treatment page eCRF pages will be used to determine the dose changes, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

The duration of the interruption will be summarized by time intervals in weeks : <1week, ≥1-<2 weeks, ≥2-<4 weeks, ≥4-<8 weeks and ≥8weeks as well as by descriptive statistics. The time intervals may be adjusted depending on the observed data.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption are entered on consecutive days with different reasons, they will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

For NIS793, tislelizumab, FOLFIRI/Modified FOLFOX + Bevacizumab, dose changes are defined as a reduction of dose from the protocol planned starting dose or a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption. In addition, for NIS793, dose change/reduction can also occur when the dosing frequency is decreased from Q2W to Q4W (DL 1 to DL-1).

2.4.1.2 Prior, concomitant and post therapies

2.4.1.2.1 Prior treatment anti-cancer therapy

The study will include adult participants who progressed on or within 6 months after the last dose of one prior line of systemic anti-cancer therapy administered for metastatic disease. The number and percentage of subjects for prior line of systemic anti-cancer therapy within 6 months after the last dose for metastatic disease before the start of study treatment will be summarized by Anatomical Therapeutic Classification (ATC) class, preferred term overall and by treatment arm. Summaries will include total number of regimens.

For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized by treatment group.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The analyses will be performed using the FAS.

2.4.1.2.2 Post treatment anti-cancer therapy

Post anti-neoplastic medications since discontinuation of study treatment will be listed and summarized by ATC class, preferred term, overall and by by treatment group by means of frequency counts and percentages. For post anti-neoplastic radiotherapy, reason for initiating of new therapy, location and time from treatment disposition (end of treatment) to the start of

new therapy will be summarized and listed by treatment group. For post anti-neoplastic surgery, time from treatment disposition to the date of surgery and procedure will be summarized and listed by treatment group.

The analyses will be performed using the FAS.

2.4.1.2.3 Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a participant coinciding with the study treatment period. Concomitant therapy includes medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing dictionary that employs the WHO-ATC classification system and summarized by lowest ATC class and PT using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All concomitant medications will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings. In addition, Surgical and medical procedures will be coded using MedDRA and summarized by SOC, preferred term and treatment arm in the safety set.

2.4.2 Safety run-in part

The analyses for study treatment / compliance in Section 2.4.1.1 will be repeated for **Safety run-in part** but by SOC cohort and dose level if applicable. All prior, concomitant and post therapies in **Safety run-in part** will be listed by SOC regimen and dose level, where the SOC regimen refers to:

- Investigational drug(s) + modified FOLFOX6 + bevacizumab
- Investigational drug(s) + FOLFIRI + bevacizumab

2.5 Analysis of the primary objectives

The primary objective of the **Safety run-in part** is to confirm the RP2D of each investigational arm (NIS793, NIS793+tislelizumab in combination with SOC)

The primary objective of **Expansion part** is to evaluate preliminary efficacy of each investigational arm (NIS793, NIS793+tislelizumab in combination with SOC anti-cancer

therapy) versus control arm (SOC anti-cancer therapy) in terms of progression-free survival (PFS) by Investigator's assessment per RECIST 1.1.

2.5.1 Primary endpoints

Safety run-in part

The primary endpoint for the **Safety run-in part** of each investigational arm is incidence of Dose Limiting Toxicities (DLT) during first cycle (i.e, 28 days, or 4 weeks) of treatments for :

Investigational arm #1,

- NIS793 and SOC anti-cancer therapy (modified FOLFOX6 + bevacizumab)
- NIS793 and SOC anti-cancer therapy (FOLFIRI + bevacizumab)

Investigational arm #2,

- NIS793, tislelizumab and SOC anti-cancer therapy (modified FOLFOX6 + bevacizumab)
- NIS793, tislelizumab and SOC anti-cancer therapy (FOLFIRI + bevacizumab)

CCI [redacted] the dose evaluation for investigational arm #2 mFOLFOX was not conducted. Thus, no data summaries were produced and the BLRM was not updated for for investigational arm #2 mFOLFOX.

Expansion part

The clinical question of interest is to estimate the treatment effect of the investigational arm as compared to control arm for the mCRC patients on prolonging PFS. The definition of the primary estimand for the **Expansion part** is detailed in Section 1.2.1. The primary endpoint is PFS, defined as the time from the date of randomization to the date of the first documented progression as per RECIST 1.1 per investigator or any-cause death. PFS will be assessed via local review according to RECIST 1.1. Censoring conventions (i.e. handling of missing values, censoring, and discontinuations) are provided in section 2.5.4.

2.5.2 Statistical hypothesis, model, and method of analysis

Safety run-in part

The primary endpoint for the **Safety run-in part** is the incidence of DLT during first 28 days.

DLT evaluation will be based on participants included in the DDS and will be guided by an algorithmic-based design. The decision on dose tolerability will be based on the totality of all relevant data from the ongoing study and a review of safety data from the DLT evaluation period. A BLRM using EWOC criteria to evaluate the risk of DLT will be used to confirm the dose of RP2D

Dose confirmation will occur if the following conditions are met:

- At least six evaluable participants treated at this dose regimen;

- This dose satisfies the EWOC criteria;
- It is the dose recommended for participants after review of all clinical, PK, and laboratory data by Novartis and Investigators in a safety review meeting.

The assessment of patient risks will be based on summaries of the posterior distribution of DLT rates for each dose. After the enrolled 10 patients complete the DLT evaluation period for each SOC cohort, the posterior distribution for the risk of DLT for both dosing regimens of NIS793 2100 mg Q2W and Q4W by SOC cohorts will be evaluated. If one of the conditions cannot be satisfied, dose confirmation will not be declared and additional 10 patients will be enrolled for dose level – 1 regimen for that SOC cohort. The same criteria of DLT assessmentss will be applied for the new dose level.

The posterior distributions will be summarized to provide the posterior probability that the risk of DLT for each dose regimen lies within the following intervals:

• Under-dosing: [0 , 0.16)

• Targeted toxicity: [0.16 , 0.33)

• Excessive toxicity: [0.33 , 1]

Dosing regimen decisions are guided by the escalation with overdose control (EWOC) principle (Rogatko et al 2007).

The possibility of excessive toxicity is of interest in this study as the objective is to confirm the safety of the proposed dose regimen. A dosing regimen may only be used for newly enrolled paticipants if the risk of excessive toxicity (within the interval [0.33, 1]) at that dosing regimen is less than 25%.

DLTs will be listed, and their incidence summarized by primary system organ class, preferred term and worst grade (CTCAE v5.0). Listings and summaries will be based on the DDS.

Expansion part

The primary efficacy objective of this study is to characterize the difference in anti-tumor activity of investigational arms comparing to control arm SOC in prolonging time to radiological progression in second line mCRC:

- Investigational arm #1: NIS793 with SOC (FOLFIRI + bevacizumab/Modified FOLFOX6 + bevacizumab)
- Investigational arm #2: NIS793 + tislelizumab with SOC (FOLFIRI + bevacizumab/Modified FOLFOX6 + bevacizumab)

The primary efficacy analysis is to compare investigational arm #1 vs control and also to compare investigational arm #2 vs control. It will compare the investigational arm against all patients randomized to control arms combined. There will be no formal hypothesis testing, and only descriptive analysis will be carried out.

The PFS distribution will be estimated using the KM method, and KM curves, medians and 95% CIs of the medians will be presented for each treatment group.

PFS will also be listed by treatment arm, including participants from **Investigational arm #1, Investigational arm #2** and **Control arm** who continue treatment beyond RECIST 1.1 progression according to local investigator assessment based on protocol specified criteria.

2.5.3 Handling of intercurrent events

For the analysis of NIS793 + SoC (investigational arm #1) vs SoC (control arm), the handling strategies for two intercurrent events are explained in the following:

- Discontinuation of study treatment for any reason: all PFS events will be included in the analysis irrespective of the study treatment discontinuation reasons (treatment policy strategy).
- Any unforeseen intercurrent events (e.g., COVID-19 pandemic related events): All PFS events will be included in the analysis irrespective of any unforeseen intercurrent events (treatment policy strategy).
- The handling strategies is same as described above for the primary analysis of NIS793 + tislelizumab + SoC (investigational arm #2) vs SoC (control arm).

2.5.4 Handling of missing values/censoring/discontinuations

Safety run-in part

Participants who are ineligible for the DDS will be excluded from the BLRM of DLT although their data will be used for all remaining analyses. Other missing data will simply be noted as missing on appropriate tables/listings.

Expansion part

I a participant has not progressed or died at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date.

If a PFS event is observed after two or more missing or non-adequate tumor assessments, then PFS will be censored at the last adequate tumor assessment before the PFS event. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used [CSP Appendix 1]. Censoring rules for PFS follow the RECIST 1.1 guidelines and details can be found in Section 2.5.7.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of complete response (CR), partial response (PR), or stable disease (SD) before an event or a censoring reason has occurred. If no post-baseline assessments are available (before an event or a censoring reason occurred), the date of treatment randomization will be used.

2.5.5 Sensitivity analysis

CCI

2.5.6 Supplementary analyses

For all supplementary estimand analyses, no statistical significance conclusion should be performed.

The following summaries will be provided: Kaplan-Meier estimates, estimate of the median PFS along with 95% confidence interval, and hazard ratio obtained using the Cox proportional hazards model.

CCI

2.5.7 Censoring pattern of PFS

The analysis of PFS will be based on the local radiological assessments up until the cut-off date defined in Section 2.1.1. The analysis will be performed on the FAS and will use the default censoring and event date options from Table 2-5 based on options A(1), B(1), C1(1), C2(1), D(1), E(1), and F(1). In particular, PFS will be censored at the last adequate tumor assessment if a patient didn't have an event or if the event occurred after two or more missing tumor assessments. PFS will not be censored if a new antineoplastic therapy is started; instead, an Intent-To-Treat approach will be used and this new antineoplastic therapy will be ignored for the purposes of PFS derivation (and tumor assessments will continue), i.e. option F(1) in Table 2-6 will be used. Discontinuation of study treatment (for any reason) will not be considered as a reason for censoring.

Table 2-5 Options for event dates used in PFS, duration of response

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1].=Definitions can be found in the Protocol Appendix.Section 16.1..3.25[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Protocol Appendix 3 Section 16.1..3.25.
[3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death

Determination of missing adequate assessments

The term 'missing adequate tumor assessment' is defined as a tumor assessment not done or tumor assessment with overall lesion response 'Unknown'. For the sake of simplicity, a 'missing adequate tumor assessment' will also be referred to as a 'missing assessment'.

As described in Table 2-6 above, the PFS censoring and event date options depend on the presence and the number of missing tumor assessments (TAs). In the analysis of PFS, an event occurring after two or more missing assessments or non-adequate tumor assessments is censored at the last adequate tumor assessment.

An exact rule to determine whether there is no, one or two missing TAs is therefore needed. This rule is based on the time interval between the last adequate tumor assessment (LATA) date and the event date. The scheduled date of tumor assessments (in weeks from randomization), protocol specified windows for tumor assessments, and the thresholds for LATA to belong to a visit can be found in the following table.

Table 2-6 Schedule for tumor assessment and time windows

Assessment schedule		Scheduled date (weeks from randomization)	Threshold (weeks)*
Every 8 weeks for the first 13 months	Baseline	0^	n/a
	C3D1	8	12
	C5D1	16	20
	C7D1	24	28
	C9D1	32	36
	C11D1	40	44
	C13D1	48	**52**
Every 12 weeks after 13 months	C16D1	60	66
	C19D1	72	78
	C22D1	84	90
	C25D1	96	102

* The mid-point between current and next visit (except for baseline) and the upper limit for LATA to be matched to a certain scheduled assessment, e.g. if LATA is at week 10, this is after threshold for C3D1 and before that for C5D1, so the matching scheduled assessment is C5D1.

^ Day of randomization is taken as 0.

To calculate the number of missing tumor assessments, the LATA before an event is matched with a scheduled tumor assessment using the time window in the table above (essentially whichever scheduled assessment it is closest to).

Two additional thresholds, D1 and D2 are calculated for that scheduled assessment based on the protocol-specified schedule and windows.

- The threshold D1 is defined as the protocol-specified time interval between the TAs plus 2x the protocol-allowed time window around the assessments.
- The threshold D2 is defined as twice the protocol-specified time interval between the TAs plus 2x the protocol-allowed time window around the assessments (except when the matched scheduled tumor assessment is C11D1, in which case D2 is defined in Rule 2 below).

Since there is a change of schedule for tumor assessments after 13 months, D1 and D2 are defined differently depending on when LATA occurs.

Rule 1: if LATA happens within 36 weeks from randomization (the matched scheduled tumor assessment is C9D1 or before). For example, D1=8+2=10 weeks and D2=2*8+2=18 weeks.

Rule 2: if LATA happens after 36weeks but within 44 weeks from randomization (the matched scheduled tumor assessment is C11D1). For example, D1=8+2=10 weeks and D2=8+16+2=26 weeks.

Rule 3: if LATA happens after 44 weeks from randomization (the matched scheduled tumor assessment is C13D1 or later). For example, D1=12+2=14 weeks and D2=2*12+2=26 weeks.

The number of missing events is defined as:

- An event after LATA+D1 weeks will be considered as having >=1 missing assessment
- An event after LATA+D2 weeks will be considered as having >=2 missing assessments

The same definition of D2 will be used to determine the PFS censoring reason. If there is no post-baseline adequate tumor assessment available (before an event or a censoring reason occurred), the randomization date will be used to compute the interval.

If the time interval between the last adequate TA date and the earliest of the following dates is smaller or equal to D2 days:

- Analysis cut-off date
- Date of consent withdrawal
- Visit date of study treatment discontinuation due to lost to follow-up or end of post-treatment follow-up discontinuation due to lost to follow-up,

then the PFS censoring reason will be respectively:

- ‘Ongoing’
- ‘Withdrew consent’
- ‘Lost to follow-up’

However if the time interval is larger than D2 days with no event then the PFS censoring reason will always default to ‘Adequate assessment no longer available’. If the time interval between the last adequate tumor assessment date and the PFS event date is larger than D2 then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

No baseline tumor assessments

As described in Table 2-6, since the timing of disease progression cannot be determined for patients with missing baseline tumor assessment, these patients are censored in the PFS analysis at the date of randomization. This rule, however, only applies to the ‘progressive disease’ component of the PFS assessment.

Patients without any baseline tumor assessment who die within D2 time interval from date of randomization will be counted as having an event in the analysis of PFS at the date of death.

All deaths will be counted in the overall survival analysis regardless of presence or absence of the baseline tumor assessment.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary objectives: Efficacy analysis

The secondary efficacy endpoints will be assessed using the FAS. The following analyses will be performed based on local investigator assessment unless otherwise specified.

For the **Safety run-in part**, the secondary efficacy endpoints are below:

- PFS by investigator per RECIST 1.1
- OS
- ORR, DCR, DOR, and TTR by Investigator assessment as per RECIST 1.1

For the **Expansion part**, the secondary efficacy endpoints are the following:

- OS
- ORR, DCR, DOR and TTR by Investigator assessment as per RECIST 1.1

2.7.1 Expansion part

2.7.1.1 Overall Survival (OS)

The second objective is to estimate the treatment effect based on the second endpoint of OS for the investigational arms compared to the control arm, for the target population irrespective of any post-treatment anti-neoplastic therapy received. Here the target population is defined by all subjects randomized in the study (FAS). OS is defined as the time from the date of randomization to the date of date of death due to any cause. The treatment of interest is the randomized treatment (investigational arm and control arm) with or without any new anti-neoplastic therapy post randomization as needed. In addition,

- The remaining **intercurrent event** describes how events that may occur after randomization are considered when assessing the treatment effect.
  - **Discontinuation of study treatment**: OS will take into account all OS events irrespective of the study treatment discontinuation reasons (treatment policy)
  - **Any unforeseen intercurrent events** (e.g., COVID-19 pandemic): OS will take into account all deaths irrespective of any unforeseen intercurrent events (treatment policy strategy).

The summary measure is the hazard ratio (HR) for OS between the two treatment arms (Investigational arm #1 vs Control arm, and Investigational arm #2 vs Control arm). It will be estimated using Cox proportional hazard model stratified by the randomization stratification factors. Median OS, with corresponding 95% CI and 25^{th} and 75^{th} percentiles and K-M

estimated for OS rate at specific timepoints (3, 6, 12, and 18 months), along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will be summarized. The corresponding K-M curves will be presented. There will be no formal hypothesis testing, and only descriptive analysis will be carried out.

2.7.1.1.1 Handling of missing values/censoring/discontinuations

In analysis, if a patient is not known to have died, then OS will be censored at the last contact date (on or before the cut-off date). Patients not known to have died will be censored for 'Lost to follow-up' if the time between their last contact date and the analysis cut-off date is longer than the protocol specified interval between the survival follow-up assessments plus 2 weeks, i.e., 18 weeks for this study. Otherwise patients will be censored as 'Alive'.

Other missing data will simply be noted as missing on appropriate tables/listings.

2.7.1.1.2 Supportive analyses

CCI

2.7.1.1.3 Censoring pattern

Number of patients with an OS event and number of patients censored for the OS analysis will be summarized. In addition, a summary of reasons for OS censoring will be provided by treatment arm.

The pattern of censored data will be examined between the treatment arms: reasons for censoring ('Alive' or 'Lost to follow-up') will be summarized by treatment arm, details in Section 2.7.1.1.1.

2.7.1.2 Progression Free Survival (PFS) comparison between Investigational arms

CCI

2.7.1.3 Overall response rate (ORR)

ORR is defined as the proportion of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as per Investigator assessment as per RECIST 1.1 [CSP Appendix 1].

ORR based on RECIST 1.1 will be calculated based on the FAS and according to the intent-to-treat (ITT) principle. ORR and its 95% exact confidence interval (Clopper 1934) will be presented by treatment arm. In addition, ORR in the subset of patient with measurable disease at baseline will be presented.

There will be no formal hypothesis testing, and only descriptive analysis will be carried out.

The BOR will be determined from response assessments undertaken while on treatment. In addition, only tumor assessments performed before the start of any further anti-neoplastic therapies (i.e. any additional secondary anti-neoplastic therapy with the exception of palliative

radiotherapy) will be considered in the assessment of BOR. A new anticancer therapy is defined as any systemic secondary anticancer therapy or any radiotherapy other than palliative for bone lesions received during or post study treatment. Palliative radiotherapy is the only setting of radiotherapy allowed during a study. It will not be considered as an antineoplastic therapy for the assessment of BOR.

BOR for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least one SD assessment (or better) > 6 weeks after randomization (and not qualifying for CR or PR).
- Non-CR/Non-PD = at least one non-CR/non-PD assessment (or better) > 6 weeks after randomization (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization (and not qualifying for CR, PR or SD).

Complete and partial responses must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Patients with 'unknown' BOR will be summarized by reason for having unknown status. The following reasons will be used:

a. No valid post-baseline assessment
b. All post-baseline assessments have overall lesion response UNK
c. New anti-neoplastic therapy started before first post-baseline assessment
d. SD or non-CR/non-PD too early
e. PD too late

Note 1: A SD or Non-CR/Non-PD is considered as "SD too early"' if the SD or Non-CR/Non-PD is documented within first 6 weeks after randomization date.

Note 2: A PD is considered as "PD too late" if the first documentation of PD is recorded more than 12 weeks after randomization date with no qualifying CR, PR or SD or Non-CR/Non-PD in between.

Note 3: Special (and rare) cases where BOR is "unknown" due to both too early SD and too late PD will be classified as "SD too early".

Waterfall plots

2.7.1.4 Disease Control Rate (DCR)

DCR is defined as the percentage of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) or stable disease (SD) as per Investigator assessment as per RECIST 1.1.

DCR will be calculated based on the data from the FAS and the corresponding 95% confidence intervals based on the exact binomial distribution (Clopper and Pearson 1934) will be presented by treatment arm.
There will be no formal hypothesis testing, and only descriptive analysis will be carried out.

2.7.1.5 Duration of response (DOR)

DOR only applies to participants whose BOR is CR or PR by Investigator assessment as per RECIST 1.1. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death. Participants continuing without progression or death will be censored at the date of their last adequate tumor assessment. Definition of last adequate tumor assessment is provided in CSP Appendix 1.

DOR will be analyzed for participants with confirmed BOR of CR or PR. If there are at least 8 participants per arm with a confirmed BOR of CR and PR the following analyses will be conducted, otherwise DOR will only be listed by treatment arm:

- Unadjusted Cox model for the overall HR and the 95% CI between treatment arm;
- Median DOR, with corresponding 95% CI and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) by treatment arm;
- K-M estimates for DOR proportions at specific timepoints (3, 6, 12, and 18 months), along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) by treatment arm;
- Summary of number (%) of events and censored participants by treatment arm.

There will be no formal hypothesis testing, and only descriptive analysis will be carried out.

2.7.1.6 Time to response (TTR)

TTR is the time from the date of randomization to the date of event defined as the first documented response of either CR or PR per RECIST 1.1, which must be subsequently confirmed (although date of initial response is used, not date of confirmation). All patients in the FAS will be included in TTR calculations. Patients without a confirmed CR or PR will be censored at the time of PFS event (i.e., disease progression or death due to any cause) for patients with a PFS event, or at the date of the last adequate tumor assessment for patients without a PFS event. Definition of last adequate tumor assessment is provided in CSP Appendix 1.

If there are at least 8 participants per arm with a confirmed BOR of CR and PR , the following analyses will be conducted, otherwise TTR will only be listed by treatment arm:

- Median TTR, with corresponding 95% CI and 25th and 75th percentiles by treatment arm (Greenwood's formula, Kalbfleisch and Prentice 2002);
- K-M estimates for TTR proportion at specific timepoints (3, 6, 12, and 18 months), along with 95% CI by treatment arm (Greenwood's formula, Kalbfleisch and Prentice 2002);
- Summary of number (%) of responses and censored participants by treatment arm.

There will be no formal hypothesis testing, and only descriptive analysis will be carried out.

2.7.2 Safety run-in Part

Best overall response (BOR), overall response rate (ORR), disease control rate (DCR), Progression-free survival (PFS) by Investigator's assessment per RECIST 1.1 and OS will be evaluated and summarized by dose cohort. Time to response (TTR) and duration of response (DOR) will be listed.

2.8 Analysis of secondary objectives: Safety analyses

All safety analyses will be based on the Safety sets for **Safety run-in part** and **Expansion part**.

For **Safety run-in part**, summary tables and listings will be presented by dose regimen (if applicable) and SOC cohort using the safety set. For **Expansion part**, all listings and tables will be presented by treatment group. For all safety analyses, the safety set will be used.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of participant's first informed consent to the day before first administration of any study treatment.

2. On-treatment period: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date),

3. Post-treatment period: starting at day 30+1 after the last administration of study treatment in the combination arm.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. Additional summaries will be displayed to report on-treatment deaths,all death, all AE, AE related to study treatment, all SAE and SAE related to study treatment collected up to 30 days after last administration of NIS793.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of the on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of participants having at least one AE, having at least one AE in each primary SOC, and for each PT using MedDRA coding. A participant with multiple occurrences of an AE will be counted only once in the respective AE category. A participant with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the ‘All grades’ column of the summary tables.

In AE summaries, the primary SOC will be presented alphabetically and the PTs will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in the investigational arm.

The following AE summaries will be produced:

- Overview of adverse events (number and % of participants with any AE, any SAE, any fatal SAE, any dose change/interruptions, AE leading to discontinuation, requiring additional therapy);
- AEs by PT;
- AEs by primary SOC;
- AEs by primary SOC and PT;
- AEs leading to study drug discontinuation regardless of study drug relationship by PT;
- AEs leading to study treatment discontinuation irrespective of causality by PT;
- AEs leading to NIS793 discontinuation regardless of study drug relationship by primary SOC and PT;
- AEs leading to Tislelizumab discontinuation regardless of study drug relationship by primary SOC and PT;
- AEs suspected to be study drug related by PT;
- AEs suspected to be study drug related by primary SOC and PT;
- AEs suspected to be NIS793 related by primary SOC and PT;
- AEs suspected to be Tislelizumab related by primary SOC and PT;
- AEs requiring additional therapy by primary SOC and PT;
- AEs leading to dose adjustment/interruption by primary SOC and PT;

In addition, a summary of serious adverse events (SAEs) with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same PT).

The following SAE summaries will be produced:

- SAEs by PT;
- SAEs suspected to be study drug related by PT;
- SAEs by primary SOC and PT;
- SAEs suspected to be study drug related by primary SOC and PT;
- SAEs suspected to be NIS793 related by primary SOC and PT;
- SAEs suspected to be Tislelizumab related by primary SOC and PT;
- SAEs with fatal outcome.

The following listings will be produced:

- All AEs;
- SAEs with fatal outcome.
- Adverse events leading to study treatment discontinuation

Considering there will be subjects who had their safety follow-up period according to the last version of protocol, i.e. 120 days, following listings will be generated:

- all AE collected up to 120 days after last administration of NIS793 or tislelizumab.

- AE related to study treatment collected up to 120 days after last administration of NIS793 or tislelizumab.
- All SAE collected up to 120 days after last administration of NIS793 or tislelizumab.
- New antineoplastic therapies collected up to 120 days after last administration of NIS793 or tislelizumab.

EudraCT and clinicaltrials.gov requirements for AEs summaries

"For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on

- on-treatment adverse events which are not serious adverse events with an incidence greater than X% and
- on-treatment serious adverse events and SAE suspected to be related to study treatment

will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT."

2.8.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest (AESI) is a grouping of AEs that are of scientific and medical concern specific to compound NIS793, tislelizumab and SOC. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), high level group terms, high level terms, and PTs. Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. An NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of participants with at least one event of the AESI occurring during on-treatment period will be summarized. As more safety data and AE/SAE data are collected, we may identify different risks and change the list of AESI.

A non-exhaustive list of AESI is provided below for investigational drug. This may change as further data becomes available.

- Renal toxicity/serum creatinine ≥ Grade 2
- Neutropenia ≥ Grade3
- Febrile neutropenia
- Immunogenicity/Hypersensitivity reactions ≥ Grade3

- Infusion reactions ≥ Grade3
- Diarrhea ≥ Grade3
- Hypertension ≥ Grade3
- Haemorrhage ≥ Grade3
- Cardiac valvulopathy (symptomatic) ≥ Grade3
- Skin reactions ≥ Grade3
- Eyelid abnormality (≥ Grade 2)

In addition, following health authority requests the following will also be assessed as AESIs:

- Covid-19 / SARs-CoV2 positive cases, irrespective of causality
- Covid-19 vaccination status in study subjects & subsequent infection incidence

Summaries of these AESI will be provided by treatment arm and SOC cohorts (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose interruption, hospitalization, death etc.). A listing of all grouping levels down to the MedDRA PTs used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment deaths by PT and all deaths (including post-treatment deaths) by primary SOC and PT will be produced.

All deaths will be listed and those from post-treatment periods will be flagged.

EudraCT and clinicaltrials.gov requirements for deaths summaries

For the legal requirements of clinicaltrials.gov and EudraCT, the number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.3 Laboratory data

Summaries will include all assessments available for the lab parameters collected no later than 30 days after the last study treatment administration date (see Section 2.1.2.3). Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline common toxicity criteria (CTC) grade (regardless of the baseline status). Each participant will be counted only for the worst grade observed post-baseline;
- Shift tables using CTC grades to compare baseline to the worst on-treatment value;
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

For a patient with multiple assessments in a time window, the worst assessment (corresponding to the highest toxicity criteria (CTC) grade) will be used. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered.

If there are multiple assessments as baseline candidate, the same baseline rule, as specified in Section 2.1.2 will be applied. The time windows are defined in Table 2-8 for selected scheduled assessments:

Table 2-8 Time windows for lab assessments

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (screening)	Before study Day 1	< Day 1
Cycle 1 Day 1	Study Day 1*	Study Day 1 to 4
Cycle 1 Day 15	Study Day 15	Study Day 12-18
Cycle 2 Day 1	Study Day 29	Study Day 26-32
Cycle 2 Day 15	Study Day 43	Study Day 40-46
Cycle 3 Day 1	Study Day 57	Study Day 47-70
.....	.....	.....
Cycle k Day 1 (with k = 4, 5…)	Study Day 28*(k-1)+1	Study Day 28*(k-1)-13 to 28*(k-1)+1+13 If last dose date is in the window, upper bound of this time window will be EOT[b] visit date + 7
EOT	EOT date	Study Day EOT – 7 days to EOT + 14 days
Safety follow-up	EOT date + 30 days	EOT date + 15 days to EOT date + 43 days

[a] Study Day 1 = first randomization date

[b] EOT will be included if EOT is performed within 7 days of permanent discontinuation of study treatment

The following listing will be produced for the laboratory data:

- Listing of all CTC grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST, and alkaline phosphatase (ALP). The number (%) of participants with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN

- TBL > 2xULN
- TBL > 3xULN
- AST and ALT =< ULN at baseline
  - ALT or AST >3x ULN & BILI >2x ULN
  - ALT or AST >3x ULN & BILI >2x ULN & ALP >=2x ULN
  - ALT or AST >3x ULN & BILI >2x ULN & ALP <2x ULN
- AST and ALT > ULN at baseline
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN)
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP >=2x ULN
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP <2x ULN

* Elevated AST or ALT defined as: >3x ULN if =< ULN at baseline, or (>3x Bsl or 8x ULN) if > ULN at baseline

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline TBILI > 2xULN, ALT> 3xULN or AST > 3xULN will be provided.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac enzymes and imaging data

In case the study requires ECG replicates, the closest ECG assessment should be used if there are two replicates or the average of the ECG parameters should be used if there are more than two replicates. A listing of ECG assessments will be produced and notable values will be flagged. Cardiac specific enzymes, Troponin I and NTproBNP assessments from blood sample will be listed and notable values will be flagged with ECG assessments.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters will be collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-9 below.

Table 2-9 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase ≥10% from baseline	decrease ≥10% from baseline
Systolic blood pressure (mmHg)	≥180 with increase from baseline of ≥20	≤90 with decrease from baseline of ≥20

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Diastolic blood pressure (mmHg)	≥105 with increase from baseline of ≥15	≤50 with decrease from baseline of ≥15
Pulse rate (bpm)	≥100 with increase from baseline of >25%	≤50 with decrease from baseline of >25%
Body temperature	>= 39.1 °C	-

The number and percentage of participants with notable vital sign values (high/low) in the on-treatment period will be presented by treatment arm.

2.9 Analysis of secondary objectives: Pharmacokinetic endpoints

Safety run-in part and Expansion part

Pharmacokinetic data analysis will be performed for Investigational drug of the study treatment (NIS793, tislelizumab). PK concentration analyses will be repeated for each Investigational drug.

Study drug-PAS (i.e. NIS793-PAS, TSL-PAS) will be used in the pharmacokinetic data analysis for NIS793 and tislelizumabconcentrations, separately.

The PK parameters that will be determined are shown in Table 2-10. PK parameters are derived based on non-compartmental methods using Phoenix WinNonlin® software version 8.0 or higher.

Table 2-10 Non-compartmental PK parameters

Cmax	The maximum (peak) observed serum/plasma drug concentration after dose administration (mass x volume-1)
Ctrough	The lowest serum/plasma drug concentration reached by a drug before the next dose is administered (mass x volume-1)

Descriptive statistics (n, arithmetic mean, coefficient of variation% (CV%) mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum, and maximum) will be presented by study drug and treatment arm for NIS-PAS and TSL-PAS for all PK parameters defined in Table 2-10 except Tmax. For Tmax only n, median, minimum, and maximum will be presented.

All individual PK parameters will be listed by study drug and treatment arm using the FAS.

PK concentrations

Descriptive statistics (n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum, and maximum) for PK concentration will be presented at each scheduled timepoint by study drug and treatment arm for NIS-PAS and TSL-PAS.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) are set to zero by the bioanalyst and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

At the time of analysis, concentration data from participants may be removed from the estimation of certain PK parameters depending on the number of available blood samples, concomitant medications, vomiting, etc. Specific timepoints might be removed from the analysis set if technical issues with the sample are reported (e.g. sampling issues, missing information). These participants and concentration data points will be identified at the time of analysis.

Missing values for any PK data will not be imputed and will be treated as missing.

2.10 Analysis of secondary objectives: Immunogenicity

To evaluate the immunogenicity of investigational drug in combination with SOC in both **SRI part** and **Expansion part**, incidence of anti-body by treatment arms will be summarized and presented. Immunogenicity analysis is applicable to investigational drugs (e.g., NIS793, tislelizumab).

2.10.1 Sample ADA status

Each IG sample is assessed in a three tiered anti-drug anti-body (ADA) testing approach. All IG samples are analyzed in the initial screening assay (first tier). Samples testing negative in the screening assay are not subject to a confirmatory assay. Samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier). Samples can test negative in either the screening or confirmatory assay but for analysis purposes they are not differentiated.

The following properties of each sample will be provided in the source data:

- Result of assay according to pre-specified confirmatory cut-point: ‘POSITIVE’, ‘NEGATIVE’, or ‘NOT REPORTABLE.
- Titer (for positive samples): numerical representation of the magnitude of ADA response;

- Presence of NAb (for positive samples, if NAb assay results are available): 'POSITIVE' or 'NEGATIVE.
- Threshold for determining treatment boosted (titer fold change (i.e. x-fold)

The following definitions apply only to non-missing samples:

- ADA-negative sample: Sample where assay result is "NEGATIVE"
- ADA-positive sample: Sample where assay result is "POSITIVE"

The following definitions apply only to post-baseline ADA-positive samples with a corresponding determinant baseline sample. To be classified as treatment-boosted or treatment-unaffected, both the post-baseline and baseline titer must be non-missing:

- Treatment-induced ADA-positive sample: ADA-positive sample post-baseline with ADA-negative sample at baseline;
- Treatment-boosted ADA-positive sample: ADA-positive sample post-baseline with titer that is at least the fold titer change greater than the ADA-positive baseline titer;
- Treatment-unaffected ADA-positive sample: ADA-positive sample post-baseline with titer that is less than the fold titer change greater than the ADA-positive baseline titer.

NOTE: PK concentrations which are flagged for exclusion will still be used to determine ADA-inconclusive and ADA-negative samples.

The following summaries of ADA sample status (n and %) will be provided using Immunogenicity prevalence set:

- ADA-positive samples (i.e. ADA prevalence) and by timepoint (including baseline). For summaries by timepoint, the denominator is the number of participants at that timepoint with a determinant sample.

2.10.2 Participant ADA status

Any IG sample collected after more than 30 days of the last dose of NIS793and tislelizumab will not be used for summaries or derivations.

Participant ADA status is defined as follows:

- Treatment-induced ADA-positive participant: participant with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample;
- Treatment-boosted ADA-positive participant: participant with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample;
- Treatment-unaffected ADA-positive participant: participant with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample;
- Treatment-reduced ADA-positive participant: participant with ADA-positive sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples;
- ADA-negative participant: participant with ADA-negative sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples;

- Inconclusive participant: participant who does not qualify as treatment-induced ADA-positive, treatment-boosted ADA-positive, treatment-unaffected ADA-positive, treatment-reduced ADA-positive, or ADA-negative.

The following summaries of ADA participant status (n and %) will be provided using Immunogenicity incidence set (for the denominator is the number of subjects in the Immunogenicity incidence set unless otherwise specified):

- Participants with ADA- negative sample at baseline;
- Participants with ADA-positive sample at baseline;
- Treatment-boosted ADA-positive participants; for % the denominator is the number of participants with ADA-positive sample at baseline;
- Treatment-induced ADA-positive participants; for % the denominator is the number of participants with ADA-negative sample at baseline;
- ADA-negative participants: denominator is the number of participants in Immunogenicity incidence set;
- ADA-positive participants (i.e. ADA incidence): calculated as the number of treatment-boosted ADA-positive and treatment-induced ADA-positive participants; denominator is the number of participants in Immunogenicity incidence set.

2.11 Analysis of exploratory objectives

Exploratory objectives will not be addressed in the Final CSR. Hence, these analyses will not be captured in the CSR SAP.

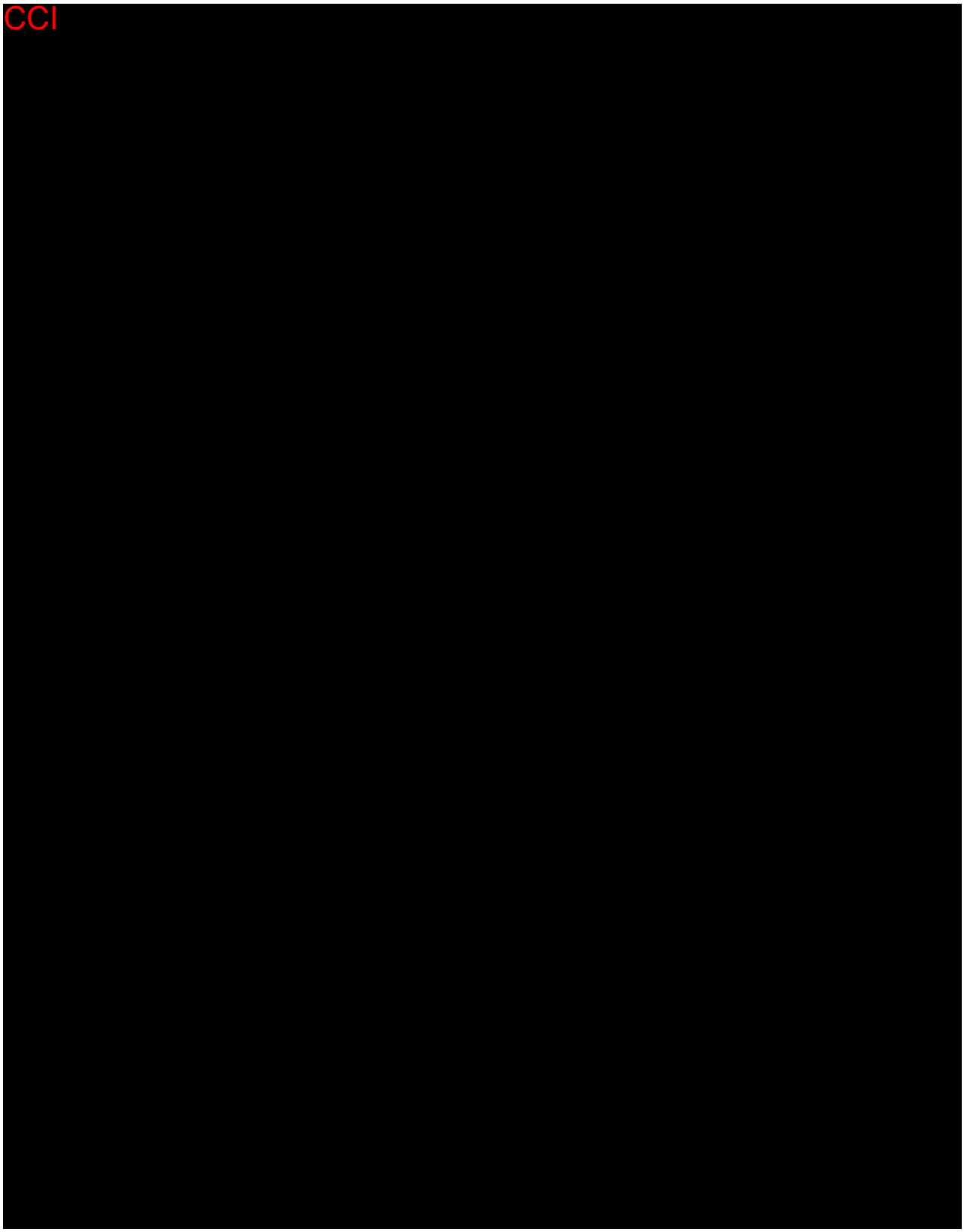
2.12 Interim analysis

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2.13 CCI [redacted]

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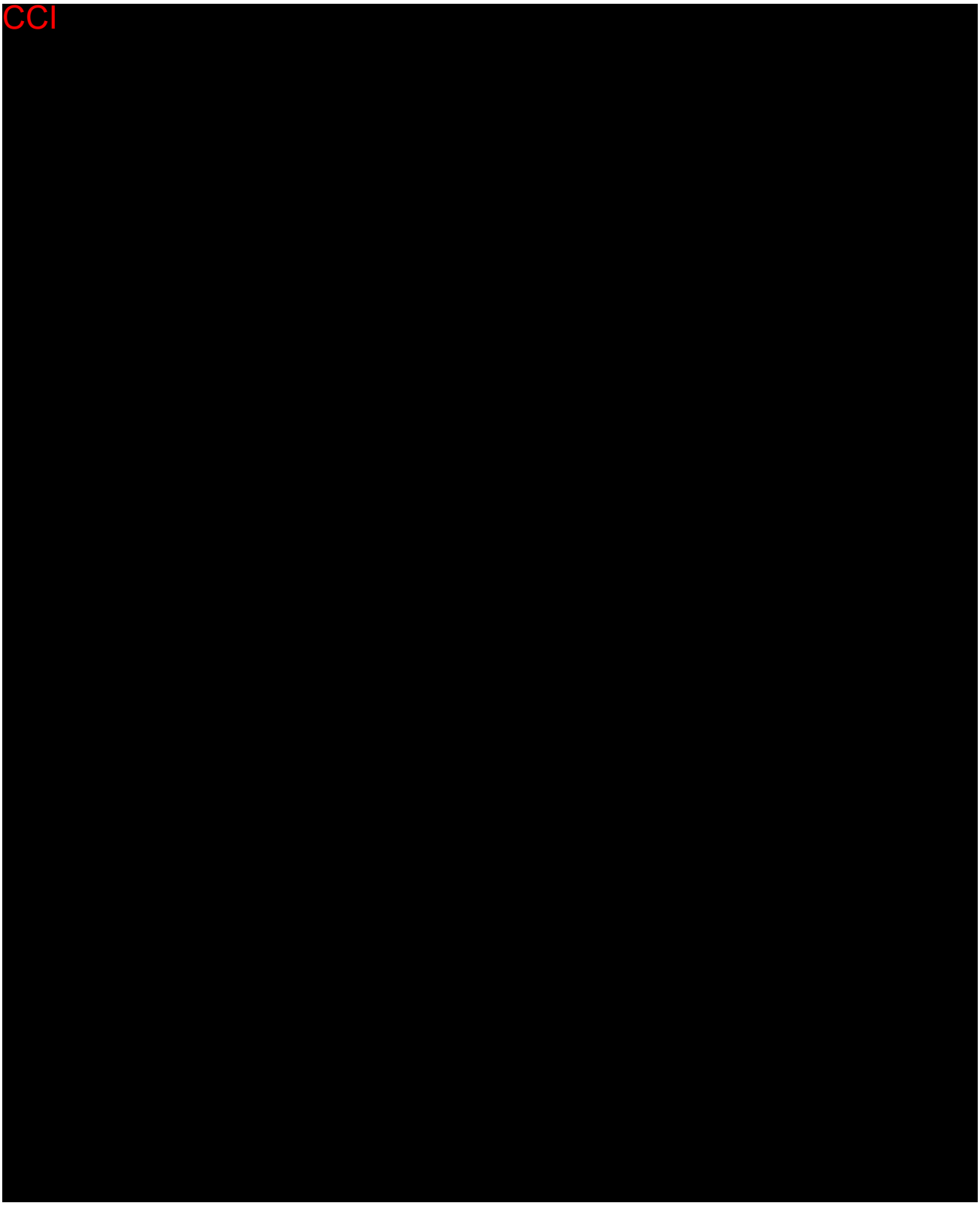
3 Sample size calculation

3.1 Primary endpoints

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4 Change to protocol specified analyses

RP2D for the investigational drug may be different for the combination with FOLFIRI and mFOLFOX6.

The RP2D for each regimen will be established when enrollment and DLT period for the respective regimen is complete, and totality of available safety, PK, and PD data has been analysed, interpreted and reviewed in the safety review meeting.

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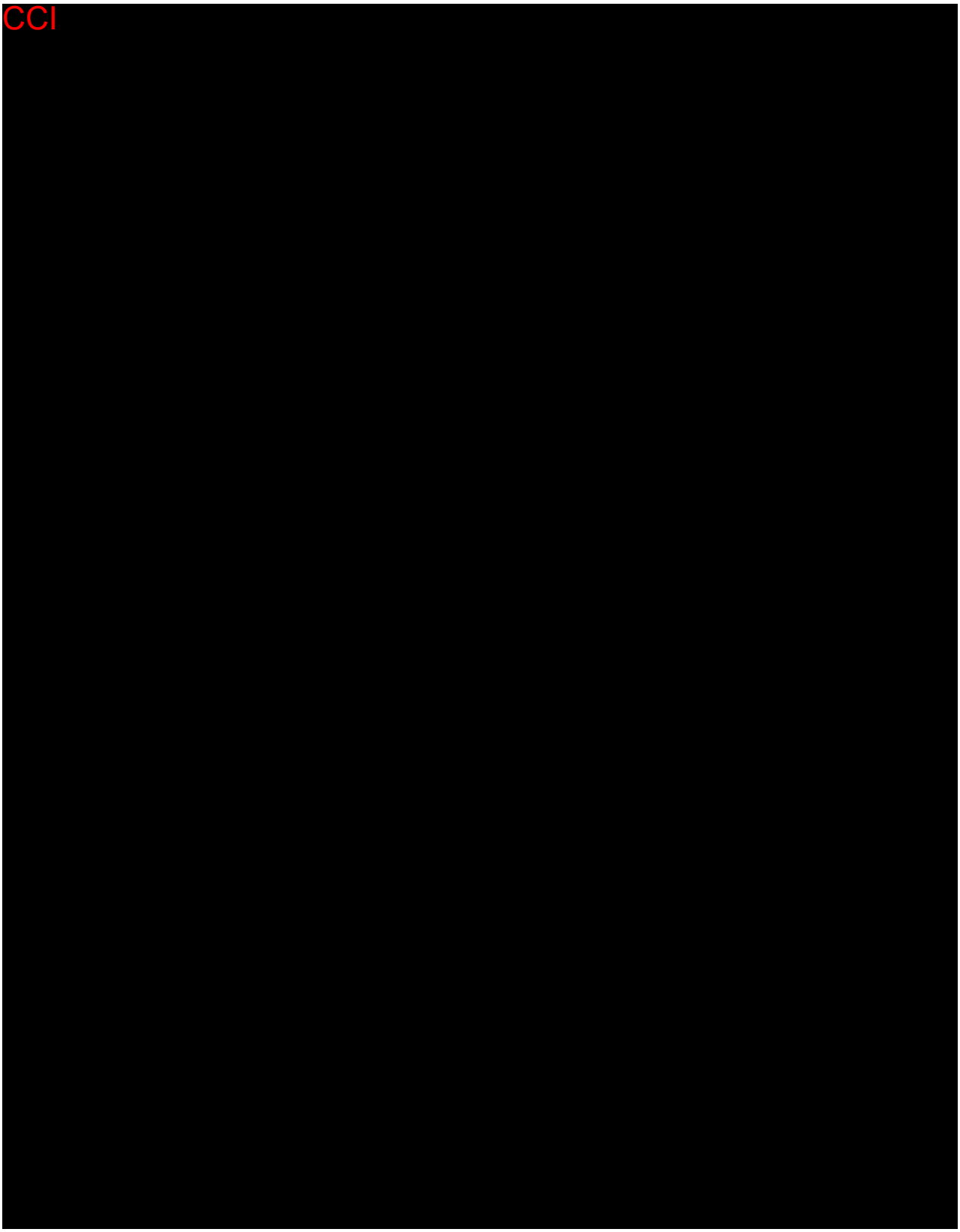
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5 Appendix

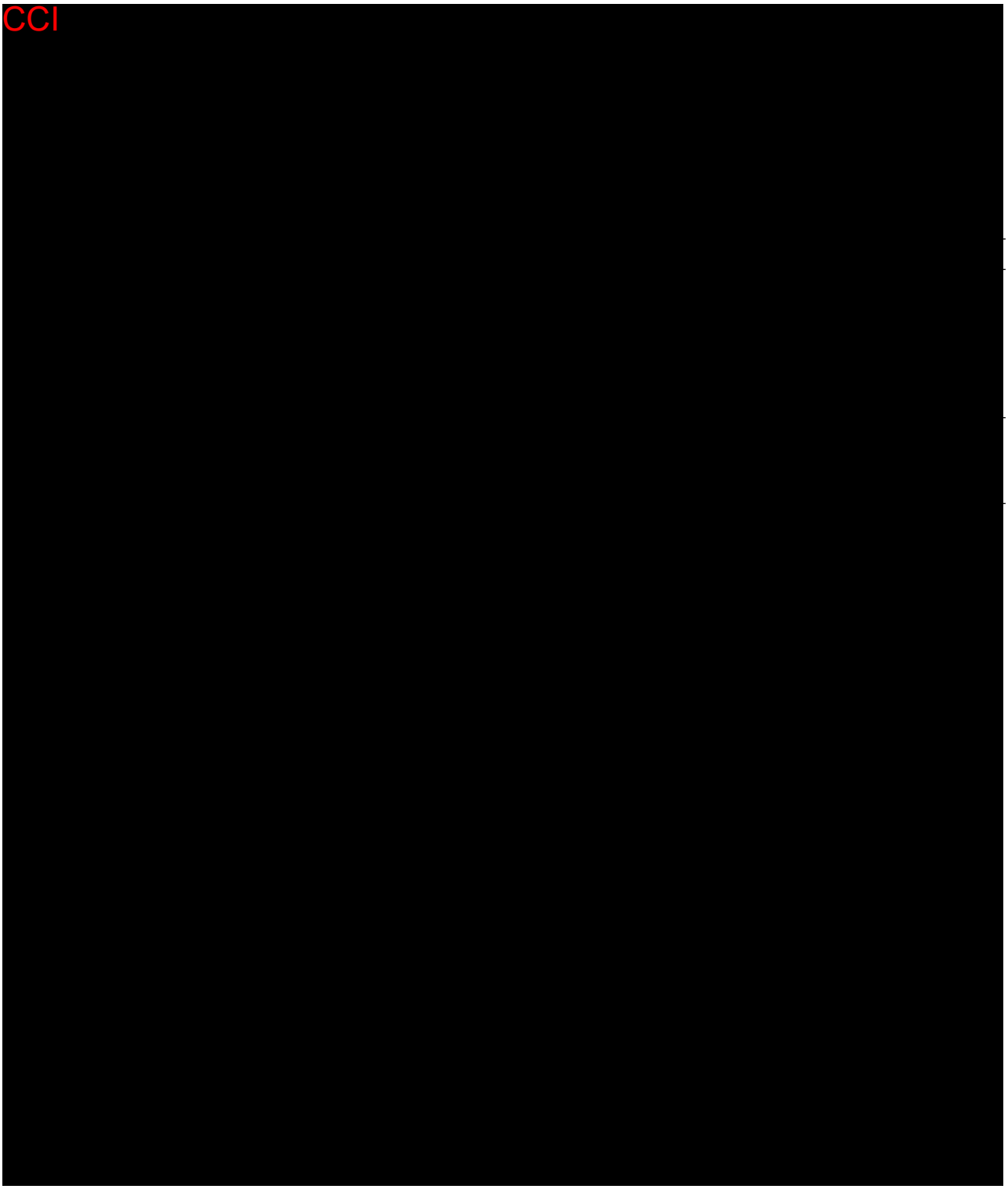
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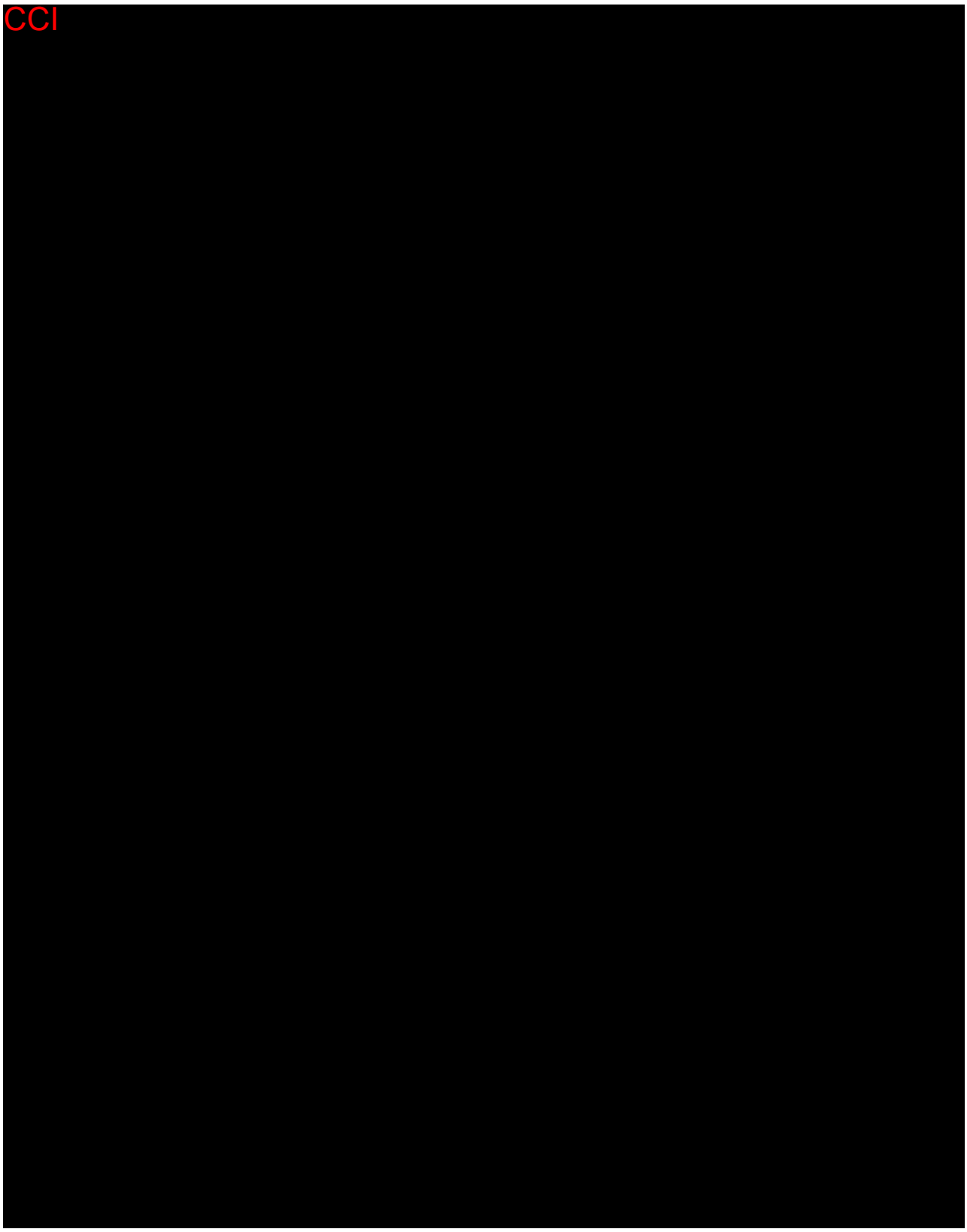
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