NOVARTIS

Clinical Development

NIS793

NIS793B12301 / NCT04935359

A randomized, double-blind, phase III study comparing NIS793 in combination with gemcitabine and nab-paclitaxel versus placebo combined with gemcitabine and nab-paclitaxel for first line treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC)

Statistical Analysis Plan (SAP)

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List of abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ATC	Anatomical Therapeutic Chemical
BLRM	Bayesian logistic regression model
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
CA19-9	Cancer Antigen 19-9
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DCR	Disease Control Rate
DI	Dose Intensity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DMS	Document Management System
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
EWOC	Escalation with Overdose Control
FAS	Full Analysis Set
HLGT	High Level Group Terms
HR	Hazard Ratio
CCI	CCI
IG	Immunogenicity
ITT	Intent to Treat
KM	Kaplan-Meier
LATA	Last tumor adequate assessment date
LFT	Liver Function Test
LLOQ	Lower Limit of Quantitation
mPDAC	Metastatic pancreatic ductal adenocarcinoma
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MID	Minimally Important Differences
MTD	Maximal tolerated dose
OS	Overall Survival
ORR	Overall Response Rate
PAS	Pharmacokinetic Analysis Set
CCI	CCI

PDI	Planned Dose Intensity
CCI	CCI
CCI	CCI
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial response
CCI	CCI
PS	Performance Status
RAP	Reporting & Analysis Process
RD	Recommended Dose
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria In Solid Tumors
RP3D	Recommended Phase 3 Dose
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SMQ	Standardized MedDRA Queries
SRT	Safety Review Team
TA	Tumor Assessments
TBL	total Bilirubin
TFLs	Tables, Figures, Listings
TTR	Time to Response
WHO	World Health Organization

Introduction

This statistical analysis plan (SAP) describes the planned analyses for the Final Clinical Study Report (CSR) of study CNIS793B12301, a randomized, double-blind, Phase III study comparing NIS793 in combination with gemcitabine and nab-paclitaxel versus placebo combined with gemcitabine and nab-paclitaxel for first line treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC).

The content of this SAP is based on protocol CNIS793B12301 v03 – Amendment 3 (18-Aug-2023).

As of 07-Jul-2023, treatment with NIS793/placebo was stopped based upon the DMC's recommendation CCI observed in the investigational treatment arm (NIS793 + gemcitabine + nab-paclitaxel). The trial was unblinded and subjects were allowed to continue with standard of care (SOC) chemotherapy (gemcitabine + nab-paclitaxel) per investigator assessment.

1 Study design

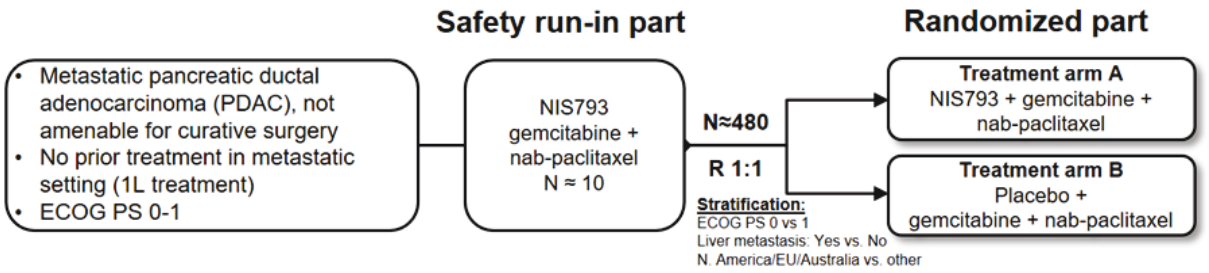
This is a randomized, double-blind, multicenter two-arm, phase III study that has two parts: a safety run-in part and a 2-arm randomized part. The study will be conducted in multiple geographical regions.

The study is expected to enroll approximately 10 patients in the safety run-in part and approximately 480 patients in the randomized part.

The decision to open the randomized part of the study will be based on dose confirmation and available safety, relevant pharmacokinetics (PK), and other clinical and laboratory data from the safety run-in part.

An overview of the study design is depicted in Figure 1-1.

Figure 1-1 Study design



Safety run-in part

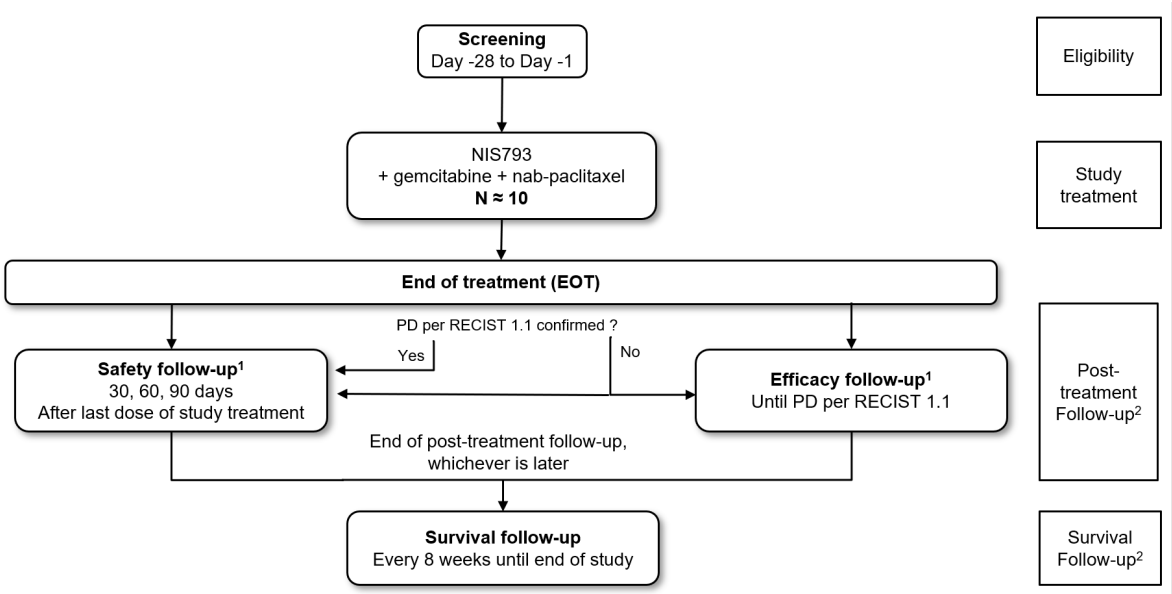
An open-label **safety run-in part** is conducted to confirm the recommended phase 3 dose (RP3D) of NIS793 in combination with gemcitabine and nab-paclitaxel. The safety run-in part will start with one treatment regimen – NIS793 (2100 mg i.v. every 2 weeks (Q2W)) in combination with gemcitabine and nab-paclitaxel. Up to approximately 10 patients will be planned to enroll in the safety run-in part in order to have at least 6 evaluable patients for the

newly investigated treatment regimen during the dose limiting toxicities (DLT) assessment period. DLT assessment period is defined as first cycle (i.e. 28 days, or 4 weeks) of dosing of the study treatment. If the starting dose is not considered tolerable and the NIS793 dose is de-escalated to the -1 dose level (2100 mg i.v. every 4 weeks (Q4W)), then an additional 10 patients will be enrolled in a cohort at NIS793 2100 mg i.v. Q4W plus gemcitabine plus nab-paclitaxel. If the lower dose is not considered safe, the study will be terminated.

Dose confirmation will be guided by an adaptive Bayesian logistic regression model (BLRM) based on any DLTs observed for the first cycle of treatment (i.e. first 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 (RD) or maximal tolerable dose (MTD) in clinical trials in patients with cancer with small sample size.

For a diagram of the study flow in the safety run-in part, see Figure 1-2. Patients will undergo safety and efficacy assessments during screening, treatment, and follow-up.

Figure 1-2 Study flow - Safety run-in part



[1] Safety follow-up and efficacy follow-up (the latest as applicable) are conducted in parallel
[2] New antineoplastic therapies collected during post-treatment follow-up and survival follow-up

Randomized part

The randomized part will enroll approximately 480 patients randomized 1:1 to the two treatment arms (~240/arm). Patients will be stratified at randomization by ECOG performance status (PS) (0 vs 1), presence of liver metastasis (yes vs no), and region (North America, Europe and Australia vs other countries).

Patients will be randomized to one of two treatment arms:

- Investigational arm (Arm A): combination of NIS793, gemcitabine and nab-paclitaxel

- Control arm (Arm B): combination of placebo, gemcitabine and nab-paclitaxel

Crossover will not be allowed during the study duration.

This is a superiority study that will compare Arm A to Arm B to support the primary objective.

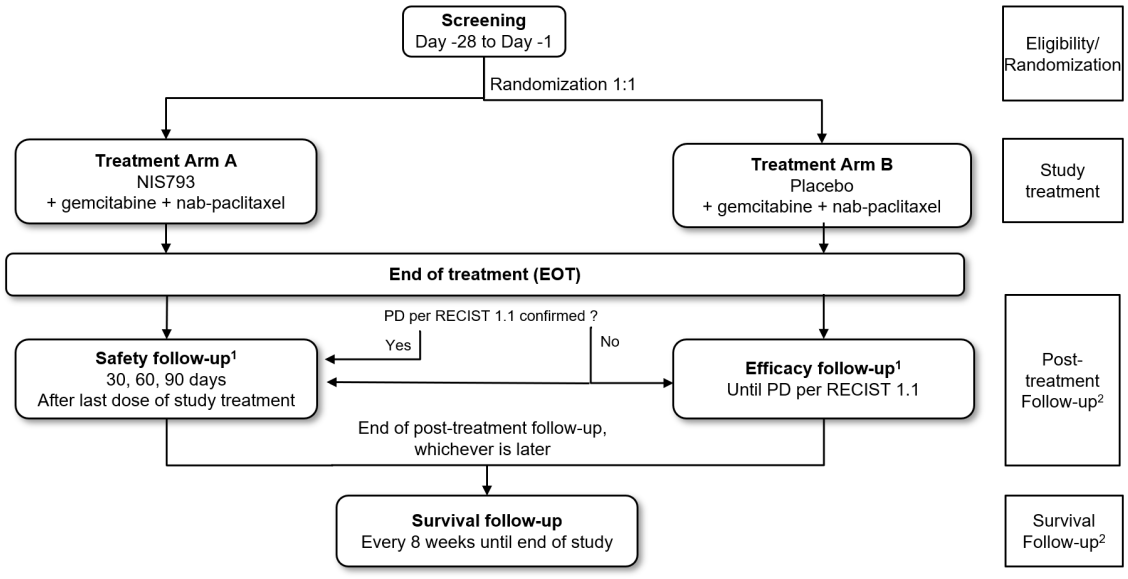
The study treatment is administered as a 28-day treatment cycle. NIS793 will be administered at a flat dose 2100 mg intravenous (i.v.) on day 1 and 15 for Q2W schedule or day 1 only for Q4W schedule for each cycle. The RP3D will be confirmed in the safety run-in part. Gemcitabine (1000 mg/m² i.v. on days 1, 8 and 15) and nab-paclitaxel (125 mg/m² i.v. on days 1, 8 and 15) will be given as per label.

Patients will be treated with study treatment until unacceptable toxicity, disease progression per RECIST 1.1, withdrawal of consent/opposition to use data/biological samples, or any other condition of treatment discontinuation conditions specified in the protocol, whichever is earlier. Chemotherapy treatment could be continued after discontinuation of NIS793 or placebo if disease has not progressed per RECIST 1.1.

As of 07-Jul-2023, the administration of NIS793/placebo was stopped for all subjects following the recommendation from DMC. Protocol amendment 3 will allow participants to continue the study following a less intense efficacy assessments and revised safety assessments as needed for standard of care only treatment.

For a diagram of the study flow in the randomized part, see Figure 1-3. Patients will undergo safety and efficacy assessments during screening, treatment, and follow-up.

Figure 1-3 Study flow - Randomized part



[1] Safety follow-up and efficacy follow-up (the latest as applicable) are conducted in parallel
[2] New antineoplastic therapies collected during post-treatment follow-up and survival follow-up

1.1 Study objectives, endpoints and estimands

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Safety run-in part:** To confirm the RP3D of NIS793 in combination with gemcitabine and nab-paclitaxel (standard of care).	• **Safety run-in part:** Incidence of DLTs during the first cycle (4 weeks) of treatment
• **Randomized part:** To compare OS in participants with mPDAC treated as the first line treatment with the combination of NIS793, gemcitabine and nab-paclitaxel to the combination of placebo with gemcitabine and nab-paclitaxel.	• **Randomized part:** OS (see Section 1.1.1 for Primary Estimand)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Safety run-in part:** To evaluate safety and tolerability of NIS793 in combination with gemcitabine and nab-paclitaxel	• **Safety run-in part:** • Safety: Incidence and severity of adverse events (AEs) including changes in laboratory parameters, vital signs, body weight and cardiac assessments • Tolerability: Dose interruptions, reductions and dose intensity
• PK of NIS793 in combination with gemcitabine and nab-paclitaxel	• PK parameters including e.g. Cmax and Ctrough for NIS793 in combination with gemcitabine and nab-paclitaxel
• Preliminary anti-tumor activity of NIS793 in combination with gemcitabine and nab-paclitaxel	• Progression-free survival (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 OS
• **Randomized part:** To evaluate the efficacy (PFS, ORR, DCR, DOR, TTR) in participants treated as the first line treatment of NIS793 in combination with gemcitabine and nab-paclitaxel versus placebo plus gemcitabine and nab-paclitaxel	• **Randomized part:** PFS, ORR, DCR, DOR and TTR by Investigator's assessment per RECIST 1.1
• To evaluate safety and tolerability in each treatment arm	• Incidence and severity of AEs and SAEs, changes in laboratory parameters, vital signs, body weight and cardiac assessments; dose interruptions, reductions and dose intensity
• To explore PK of NIS793 in combination with gemcitabine and nab-paclitaxel	• CCI [redacted], NIS793 serum concentrations over time and derived PK parameters (e.g. Cmax, AUC)

Objective(s)	Endpoint(s)
	For participants CCI [redacted], PK parameters including Cmax, Ctrough and $Ctrough_{ss}$ for NIS793
• To characterize the incidence of immunogenicity of NIS793 in combination with gemcitabine/nab-paclitaxel	• Anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI [redacted]	

Objective(s)	Endpoint(s)
CCI	

1.1.1 Primary estimand(s)

The primary estimand is specified for the randomized 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).

The primary scientific question of interest is to estimate the treatment effect on the primary endpoint of OS of NIS793 in combination with gemcitabine and nab-paclitaxel (arm A) compared to placebo in combination with gemcitabine and nab-paclitaxel (arm B) for the target population, regardless of discontinuation from study treatment, or start of a new subsequent antineoplastic therapy.

The primary estimand is described by the following five attributes:

1. Population: all randomized patients with mPDAC treated with the first line treatment. Further details on the population characteristics are provided in the eligibility criteria.

2. Treatment: randomized treatments, i.e. NIS793 in combination with gemcitabine/nab-paclitaxel or placebo and gemcitabine/nab-paclitaxel with or without any new subsequent antineoplastic therapy as needed.

3. Variable: OS defined as the time from the date of randomization to the date of death due to any cause.

4. Handling of remaining intercurrent events:

- Discontinuation of study treatment for any reason: OS will take into account all deaths irrespective of the study treatment discontinuation reasons (treatment policy)
- Any unforeseen intercurrent events (e.g., Coronavirus disease 2019 (COVID-19) -related events) will be handled by treatment policy strategy.

5. Summary measure: hazard ratio (HR) for OS between the two treatment arms A and B. It will be estimated using Cox proportional hazard model stratified by randomization stratification factors. The primary comparison will be performed using log-rank test stratified by randomization stratification factors.

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 will be used to perform all data analyses and to generate tables, figures and listings. R-3.6.1 will be used to perform the BLRM analysis.

2.1.1 Data included in the analysis

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) with NIS793 in combination with gemcitabine and nab-paclitaxel, lost to follow-up, died, withdrew consent or discontinued the study, the BLRM will be updated to calculate the posterior probabilities of DLT rates in 'underdose', 'targeted toxicity' and 'excessive toxicity' intervals. The dosing regimen may only be used as RP3D for the randomized 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, CCI and BLRM inference and results will be reviewed in a Safety Review Team (SRT) meeting. The reporting and analysis details will be documented in a standalone SAP. 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 primary and/or final CSR.

2.1.1.2 Randomized Part

For the final CSR, a unique cutoff date will be established when the last patient last visit occurs.All statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an AE) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

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. This approach applies, in particular, to AE and concomitant medication reports. For these cases, the end date will not be imputed and therefore will not appear in the listings.

As of 7-Jul-2023, the administration of NIS793/placebo was stopped for all subjects following the recommendation from DMC. Post implementation of protocol amendment 3, CCI [redacted], and no hypothesis testing will be performed.

2.1.1.3 General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to the expected small number of patients 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; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

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

2.1.2 General definitions

2.1.2.1 Investigational drug and study treatment

Investigational drug refers to NIS793.

Study treatment refers to NIS793 in combination with gemcitabine and nab-paclitaxel, or NIS793 matching placebo in combination with gemcitabine and nab-paclitaxel.

NIS793 matching placebo will be referred to as "placebo" in the remainder of this document.

2.1.2.2 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 (NIS793/placebo, gemcitabine or nab-paclitaxel) was administered as per the Dosage Administration (e)CRF. 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/placebo is taken on 01OCT2021, and first dose of gemcitabine or nab-paclitaxel is taken on 03OCT2021, then the date of first administration of study treatment is 01OCT2021.

2.1.2.3 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 (NIS793/placebo, gemcitabine or nab-paclitaxel) was administered as per Dose Administration (e)CRF.

For example: if the last dose of NIS793/placebo is taken on 15FEB2022, and the last dose of gemcitabine or nab-paclitaxel is taken on 17FEB2022, then the date of last administration of study treatment is on 17FEB2022.

2.1.2.4 Last date of exposure to study drug/treatment

The study treatment schedule is organized in cycles of 28 days. The last date of exposure to study treatment is derived to be the latest date of the last date of exposure to NIS793/placebo, gemcitabine and nab-paclitaxel. The last date of exposure to study drug (NIS793/placebo, gemcitabine or nab-paclitaxel) will be derived as follows:

- the last date of exposure to study drug is calculated as (last date of administration of study drug) + (length of time interval - 1)
- For NIS793/placebo administered on a Q2W schedule, the length of time interval is 14 days, and the last date of exposure to study drug is then [last date of study drug administration + (14-1)].

- If the dose frequency for NIS793/placebo shifts from Q2W to Q4W, the last date of exposure to NIS793/placebo will be derived using the same definition specified above by replacing 14 days with 28 days.

- For gemcitabine and nab-paclitaxel, the last date of exposure will be derived using 7 days as length of time interval.

- If the patient died or was lost to follow-up or withdrew consent the last date of exposure to study drug is the earliest of the date calculated as above, date of death or the date of last contact.

If the derived last date of exposure to study drug/study treatment goes beyond the data cutoff date, it should be truncated to the date of data cutoff. 'Date of last administration of study drug' and 'Date of last contact' are defined in Section 2.1.2.3 and 2.1.2.10 respectively.

2.1.2.5 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 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 event precedes the reference start date.

In the **Safety run-in part**, the reference start date for all assessments is the start of study treatment.

In the **Randomized part**, the reference start date for safety assessments (e.g. AE onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, PK etc.) is the start of study treatment; and the reference start date for all other, non-safety assessments (i.e. survival, ECOG PS) and CCI 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.

2.1.2.6 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.

2.1.2.7 Baseline

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

In the **Randomizated part**, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as "baseline" assessment for efficacy. In the context of baseline definition, the efficacy evaluations also CCI and

ECOG PS. [redacted] For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as ‘‘baseline” assessment.

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

For cases where time of assessment and time of treatment start is captured (e.g. pre-dose ECG, laboratory assessments, [redacted]), the last available assessment before the treatment start date/time is used for baseline.

2.1.2.8 On-treatment assessment/event and observation periods

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

1. ***pre-treatment period***: from day of patient’s informed consent to the day before first dose of study treatment
2. ***on-treatment period***: day of first dose of study treatment up to 30 days after the date of last non-zero administration of any study treatment
3. ***post-treatment period***: starting at day 31 after date of last administration of study treatment.

Participants must be followed-up for AEs and SAEs for 30 days after last dose of SOC chemotherapies and up to 90 days after last dose of NIS793, whichever is later.

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, and additional summaries will be produced for related AEs and SAEs occurring up to 90 days after last dose of NIS793.All the AEs/SAEs occurring during the 90 days period after last dose of NIS793 will be listed.

2.1.2.9 Windows for multiple assessments

Time windows will be defined for descriptive summary of [redacted], ECOG PS, and other assessments data by visit. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to the visit will be considered.

Table 2-1 Time windows for ECOG PS, Immunogenicity and vital signs assessments

Time Window	Planned Visit Timing	Time Window Definition
For ECOG PS and vital signs:		
Baseline	On or before Study Day 1	≤ Study Day 1
C2D1	Study Day 29	Study Days 1 to 42
C3D1	Study Day 57	Study Days 43 to 70

.....	.....	.....
Cycle k Day 1	Study Day 28*(k-1)+1	Study Day
(with k = 4, 5…)		28*(k-1)-13 to 28*(k-1)+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
For Immunogenicity:		
C1D1	Study Day 1	≤ Study Day 1
C2D1	Study Day 29	Study Days 1 to 42
C3D1	Study Day 57	Study Days 43 to 70
C4D1	Study Day 85	Study Days 71 to 98
C6D1	Study Day 141	Study Days 127 to 154
Cycle k Day 1	Study Day 28*(k-1)+1	Study Day
(with k = 12, 18…)		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 + 30 days	EOT date + 15 days to EOT date + 45 days
Safety follow-up2	EOT date + 60 days	EOT date + 46 days to EOT date + 75 days
Safety follow-up3	EOT date + 90 days	EOT date + 76 days to EOT date + 90 days

2.1.2.10 Last contact date

The last contact date will be derived for patients 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 patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition
Laboratory/PK/CCI collection dates	Sample collection marked as ‘done’.

Source data	Conditions
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term
Imaging assessment date	Imaging marked as done
CCI	Available assessment date

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 patient 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 dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring from 'Survival information' eCRF (Section 5.1.2.1).

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

2.2 Analysis sets

2.2.1 Analysis Set Definition

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

2.2.1.1 Full analysis set

Safety Run-in Part

For the safety run-in part, the Full Analysis Set (FAS) comprises all patients that received any study drug. According to the intent-to-treat (ITT) principle, patients will be analyzed according to the treatment(s) received.

Randomized Part

The FAS comprises all patients to whom study treatment has been assigned by randomization. According to the ITT principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

2.2.1.2 Safety set

Safety Run-in part

The Safety set includes all patients 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)). Patients will

be analyzed according to the treatment(s) received. For safety run-in part, safety set is the same as FAS.

Randomized part

The Safety set includes all patients 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)). Patients in the randomized part will be analyzed according to treatment received (NIS793 or placebo plus combination partners), where treatment received is defined as:

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

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

Patients who started treatment after the DMC recommendation to stop use of NIS793 and neither received NIS793 nor placebo, these patients will be included in the SoC (i.e. placebo) summaries as 'treatment received'.

2.2.1.3 Dose-Determining Set

Safety Run-in part

The Dose-determining set (DDS) consists of all patients in the **Safety Run-in part** who met the minimum exposure criteria and have sufficient safety evaluations after 4 weeks of treatment or experienced a DLT during the first 4 weeks of treatment.

A patient is considered to have met the minimum exposure criteria if the patient has received 2 doses of NIS793 (2100 mg i.v. Q2W) for the first cycle or 1 dose of NIS793 (2100mg Q4W) for the lower dose cohort, and at least 66% of planned dose of chemotherapy in the first cycle (the planned dose consists of 3 doses of gemcitabine (1000 mg/m^2 i.v. Days 1, 8, and 15, Q4W), and 3 doses of nab-paclitaxel (125 mg/m^2 i.v. Days 1, 8, and 15, Q4W)).

Patients 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 both the Sponsor and Investigators to have enough safety data to conclude a DLT did not occur.

2.2.1.4 Pharmacokinetic analysis set

For both safety run-in and **randomized part**, one Pharmacokinetic analysis set (PAS) will be considered for NIS793.

The PAS includes all patients who provided at least one evaluable PK concentration. For a concentration to be evaluable, patients are required to:

- Receive at least one dose (complete infusion) of the planned treatment prior to sampling
- Provide at least one valid PK concentration
- For pre-dose samples, have the sample collected before the next dose administration
- For end-of-infusion samples, have the sample collected within 1 hour post infusion

Patients may be excluded from the assessment of PK parameters if available data is insufficient. These patients will be identified at the time of analysis. More details will be defined in Section 2.7.

2.2.1.5 Immunogenicity analysis set

For both safety run-in and **randomized part**, the immunogenicity (IG) set includes two parts: IG prevalence set and IG incidence set:

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

2.2.1.6 Protocol deviations that leads to analysis set exclusion

Patients who have certain protocol deviations may be excluded from analysis.

Table 2-3 Protocol deviations leading to analysis set exclusion

Severity code	Summary of the Protocol Deviation
2	Reconsent of the patient has not been obtained for an amended ICF
5	Patient has not had at least one dose of study treatment*
8	Patient not correctly consented in initial ICF
18	Minimum exposure to study drug/safety evaluation not satisfied and no DLT in cycle 1 for the safety run-in part*

* Not considered as protocol deviation, but will evaluate the exclusion of analysis set

Table 2-4 Description of severity codes

Severity code	Actions
2	Exclude from data analysis from this point
5	Exclude from all safety analyses
8	Exclude from all analysis
18	Exclude from dose determining analysis set

Table 2-5 Determination of analysis set membership

Analysis set	Protocol deviation severity codes leading to exclusion
Full analysis set	8, 2
Safety set	5, 8, 2
Dose determining set	18, 8, 2
Pharmacokinetic analysis set	8, 2

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Randomized part

The FAS will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment arm and for all patients. In addition, listings will be reported by treatment arm. No inferential statistics will be provided.

2.3.1.1 Enrollment status

The following summaries will be provided separately for the FAS overall, and for both treatment groups:

1. Number (%) of patients who were randomized
2. Number (%) of patients who received at least one dose of study treatment after randomization

For patients who are screen failures, the reasons for not completing screening will be summarized based on "Screening Phase Disposition" eCRF.

2.3.1.2 Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm using the FAS and safety set. Categorical data (e.g. gender, age groups: <65 years vs. ≥65 years, CA 19-9 at baseline: <10,000 U/mL vs. =>10,000 U/mL, ECOG PS, liver metastasis, region at enrollment) 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 surface area (BSA), 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) and BSA (m^2) will be calculated using the Mosteller Formula Section 2.4.1.1.2 using weight and height at Baseline.

2.3.1.3 Baseline stratification factors

The number (%) of patients in each randomization stratum based on data obtained from the CRF will be summarized overall and by treatment arm for the FAS. Discordances between the actual stratum recorded in the clinical database through the data collected on eCRF and the stratum recorded in IRT at the time of randomization will be cross-tabulated.

2.3.1.4 Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer, time since initial diagnosis to the date of randomization, details of tumor histology/cytology, stage at initial diagnosis, time from first recurrence/progression to the date of randomization, time from most recent relapse/progression to the date of randomization and metastatic sites.

2.3.1.5 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will listed by treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable listings.

2.3.1.6 Patient disposition

The number (%) of randomized patients included in the FAS will be presented overall and by treatment arm. The number (%) of screened and not-randomized patients and the reasons for screening failure will also be displayed. The number (%) of patients who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment arm.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who were randomized (based on data from IRT system)
- Number (%) of patients who were randomized but not treated (based on 'DAR' eCRF page not completed for any study treatment component)
- Primary reason for not being treated (based on "Treatment disposition" eCRF page)
- Number (%) of patients who were treated (based on 'DAR' eCRF pages of each study treatment component completed with non-zero dose administered)
- Number (%) of patients who discontinued study treatment (based on the 'Treatment disposition' page)
- Primary reason for study treatment phase discontinuation (based on the 'Treatment disposition' page)
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'post-treatment follow-up disposition' page)
- Reasons for discontinuation from the post-treatment follow-up (based on 'post-treatment follow-up' page)

2.3.1.7 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 for the FAS. Protocol deviations leading to exclusion from analysis sets will be tabulated separately overall and by treatment arm as specified in Section 2.2. All protocol deviations will be listed.

2.3.1.8 Analysis sets

The number (%) of patients in each analysis set will be summarized by treatment arm and randomization stratum.

2.3.2 Safety run-in part

The following analyses will be reported in summary tables by dose cohort for the safety run-in part using the analysis details specified for the randomized part in Section 2.3.1:

- Number (%) of patients treated will be summarized by country, center and dose cohort
- Basic demographic and background data
- Diagnosis and extent of cancer
- Patient disposition and screening disposition
- Analysis sets

In addition, medical history and protocol deviations will be listed by dose cohort.

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

2.4.1 Randomized part

2.4.1.1 Study treatment / compliance

Duration of study treatment exposure, cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment. The number of patients with dose change, interruptions, discontinuation and the corresponding reasons, will be summarized and listed. Details of the derivations and summaries are provided in the following sections.

The safety set 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 5.1.2.2.

Note: As of 07-Jul-2023, NIS/Placebo is no longer being administered.

2.4.1.1.1 Duration of study treatment exposure

Duration of exposure to study drug (for NIS793/placebo, gemcitabine and nab-paclitaxel) is defined according to dosing regimen for each study drug as outlined in Section 2.1.2.1.

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

Duration of exposure to study treatment is considered by taking into account the duration of exposure to each study drug:

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

The duration includes the periods of temporary interruption. ‘Date of first administration of study drug/treatment’ and ‘last date of exposure to study drug/treatment’ are defined in Sections Sections 2.1.2.2 to 2.1.2.4.

Duration of exposure to study drug/treatment will be categorized into time intervals (<1 month, at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 12 months, at least 18 months, and ≥24 months). In addition, summary statistics will be displayed.

Note: If the last record in DAR CRF is a zero dose, this record will not be used in the analyses. For patients who have ongoing treatment, see Section 5.1.2.2.

2.4.1.1.2 Cumulative dose

Cumulative dose for any component of study treatment is defined as the total dose of the medication given during the study treatment exposure.

Cumulative dose will be summarized using descriptive statistics by treatment arm for each component of study treatment. For patients who do not receive any drug the cumulative dose will be set to zero.

The cumulative dose is calculated from the DAR eCRF.

For standard of care treatments (gemcitabine, nab-paclitaxel) with the prescribed dose recorded in unit 'mg' on CRF pages, the dose will be converted to unit mg/m^2 by dividing the prescribed dose by the BSA. The weight measured at the beginning of each cycle will be used. The BSA formula is as follows:

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

Where Wt = the last non-missing weight at the beginning of each cycle

Ht = baseline Height

2.4.1.1.3 Dose intensity and relative dose intensity

The DI and the RDI for each study treatment (NIS793, gemcitabine and nab-paclitaxel) 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 i.v. Q2W, PDI is 2100*2 = 4200 mg/cycle.
  For NIS793 2100 mg i.v. Q4W, PDI is 2100 mg/cycle.
  For gemcitabine (planned dose: 1000 mg/m^2 i.v. Days 1, 8, and 15 of each 28-day cycle), PDI is 1000×3 = 3000 mg/m^2/cycle
  For nab-paclitaxel (planned dose: 125 mg/m^2 i.v. Days 1, 8, and 15 of each 28-day cycle), PDI is 125×3 = 375 mg/m^2/cycle
- **DI** for patients with non-zero duration of exposure is defined as follows:
  DI =(actual cumulative dose) / (number of cycles on treatment)

  For NIS793/placebo Q2W:

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

  For NIS793/placebo Q4W:

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

For standard of care treatments (gemcitabine, nab-paclitaxel) scheduled for Days 1, 8 and 15 of every 28-day cycle, with the last non-zero administration of gemcitabine or nab-paclitaxel at CuDv (Cycle u Day v):

If v = 1, number of cycles on treatment = (u - 1) + 1/3

If v = 8, number of cycles on treatment = (u - 1) + 2/3

If v = 15, number of cycles on treatment = u

- **RDI**) is defined as follows:

  RDI = DI (dose unit/cycle) / PDI (dose unit/cycle), for NIS793/placebo, gemcitabine and nab-paclitaxel.

2.4.1.1.4 Dose changes, interruptions or permanent discontinuations

The number of patients who have dose changes, dose interruptions and dose permanent discontinuations and the corresponding reasons, will be summarized separately for each of the study treatment components.

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 that are entered on consecutive cycles with different reasons will be counted as separate interruptions.

For NIS793/placebo, gemcitabine and nab-paclitaxel, 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/placebo, 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 anti-cancer therapy

The number and percentage of subjects who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized by treatment arm. Prior anti-neoplastic medications will be summarized by Anatomical Therapeutic Chemical (ATC) class, PT and treatment arm.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD.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 summarized by ATC class, PT, overall and by treatment arm by means of frequency counts and percentages. 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 patient coinciding with the study treatment period. Concomitant therapy includes medications (other than study treatment) 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 (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and PT using frequency counts and percentages. These summaries will include:

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

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 dose cohort. All prior, concomitant and post therapies in safety run-in part will be listed by dose cohort.

2.5 Analysis supporting primary objective(s)

The primary objective of the safety run-in part is to confirm the RP3D of NIS793 in combination with gemcitabine and nab-paclitaxel (standard of care).

The primary objective of the randomized part is to compare OS between NIS793 plus gemcitabine plus nab-paclitaxel and placebo plus gemcitabine plus nab-paclitaxel in mPDAC patients as first line treatment.

2.5.1 Primary endpoint(s)

Safety run-in part

The primary endpoint for the safety run-in part is the incidence of DLT during first cycle (i.e, 28 days, or (4 weeks) of treatments for NIS793, gemcitabine and nab-paclitaxel).

Randomized part

The clinical question of interest is to estimate the treatment effect of the combination of NIS793, gemcitabine and nab-paclitaxel (Arm A) as compared to the combination of placebo, gemcitabine and nab-paclitaxel (Arm B) on OS in mPDAC patients. The definition of the primary estimand for the randomized phase is detailed in Section 1.1.1. The primary endpoint is OS, defined as the time from the date of randomization to the date of death due to any cause. If a patient is not known to have died, then OS will be censored at the last contact date the patient is known to be alive.

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 the first 28 days.

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 the EWOC criteria to evaluate the risk of DLT will be used to confirm the dose of RP3D.

The recommended dose regimen is confirmed when the following conditions are met:

1. At least 6 patients at this dose from DDS
2. This dose satisfies the EWOC criteria
3. The selected regimen is recommended either per the model or by review of all clinical data by the members of the SRT.

The assessment of patient risks will be based on summaries of the posterior distribution of DLT rates for each dose. After the patients enrolled to the Q2W NIS793 cohort complete the DLT evaluation period, the posterior distribution for the risk of DLT for both dosing regimens of NIS793 2100 mg i.v. Q2W and Q4W in combination with gemcitabine and nab-paclitaxel will be evaluated. If the Q2W regimen does not satisfy the criteria to be declared RP3D, then additional patients will be enrolled for dose level – 1 regimen. The same criteria of DLT assessments 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:

CCI [redacted]

[redacted]

[redacted]

Dosing regimen decisions are guided by the 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 participants if the risk of excessive toxicity (within the interval CCI [redacted]) at that dosing regimen is less than CCI [redacted].

DLTs will be summarized by primary SOC, PT and worst grade (CTCAE v5.0). Summaries will be based on the DDS.

Randomized part:

The following null and alternative hypothesis will be tested to address the primary efficacy objective for OS of Arm A (NIS793 in combination with gemcitabine and nab-paclitaxel) vs Arm B (placebo in combination with gemcitabine and nab-paclitaxel):

$H_0: \theta \geq 1$ vs $H_A: \theta < 1$

where θ is the OS HR of Arm A vs Arm B. The null hypothesis will be tested with a stratified log-rank test at an overall one-sided 2.5% significance level. The stratification will be based on the randomization stratification factors from local CRF pages: ECOG PS (0 vs. 1); liver metastasis (yes vs. no); region at enrollment (North America, Europe and Australia vs. other countries).

Analyses will be based on the FAS population according to the randomized treatment group. The OS distribution will be estimated using the KM method, and KM curves, medians and two-sided 95% CIs of the medians will be presented for each treatment group. The HR for OS will be calculated, along with its two-sided 95% CI, from a stratified Cox model using the same stratification factors as for the log-rank test.

CCI

Post implementation of protocol amendment 3, CCI , and no hypothesis testing will be performed.

2.5.3 Handling of intercurrent events

The different intercurrent events and the handling strategies are explained in the following:

1. Discontinuation of study treatment for any reason: OS will take into account all deaths irrespective of the study treatment discontinuation reasons (treatment policy strategy)
2. Any unforeseen intercurrent events (e.g., COVID-19 pandemic related events): OS will take into account all deaths irrespective of any unforeseen intercurrent events (treatment policy strategy)

2.5.4 Missing values not related to intercurrent event

Handling of patients who are ineligible for the DDS will be excluded from the BLRM of safety run-in part, although their data will be used for the primary/final CSR.

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.

2.6 Analysis supporting secondary objectives: Efficacy analyses

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

Safety run-in part:

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

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

Randomized part:

- For the randomized part, the secondary objectives for the randomized part are to compare PFS, ORR and other tumor related efficacy (DCR, TTR and DOR) based on RECIST 1.1 between NIS793, gemcitabine and nab-paclitaxel (Arm A) vs. the placebo, gemcitabine and nab-paclitaxel (Arm B).

2.6.1 Randomized part

2.6.1.1 Progression survival free (PFS)

The second objective is to estimate the treatment effect based on the second endpoint of PFS for the combination of NIS793 with gemcitabine and nab-paclitaxel compared to the combination of placebo with gemcitabine and nab-paclitaxel, for the target population irrespective of any post-treatment anti-neoplastic therapy received. Here the target population is defined by all patients randomized in the study (FAS). PFS is defined as the time from the date of randomization to the date of the first documented disease progression based on local investigator assessment as per RECIST 1.1 or date of death due to any cause, whichever occurs first. The treatment of interest is the randomized treatment (NIS793 arm or the matching placebo 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**: PFS will take into account all PFS events irrespective of the study treatment discontinuation reasons (treatment policy)
  - Any unforeseen intercurrent events due to COVID-19 pandemic will be handled by treatment policy strategy.

The summary measure is the HR for PFS between the two treatment arms. It will be estimated using Cox proportional hazard model stratified by the randomization stratification factors. PFS will be tested using the log-rank test stratified by randomization stratification factors from local CRF pages.

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

estimate along with two-sided 95% CIs will be presented at different time points (i.e. 2, 4, 6, 8, 10, 12, 14, 16, 18 and 24 months) for each of the two treatment arms.

2.6.1.1.1 Handling of missing values/censoring/discontinuations

A patient whose disease has not progressed or died by the date of the analysis cut-off will have their PFS censored at the time of the last adequate tumor evaluation performed on or before the cut-off date. Clinical deterioration will not be considered as documented disease progression. PFS events will be included in the analysis if it occurs after one missing assessment. PFS will be censored at the last adequate tumor assessment (LATA) if a patient didn't have an event or the event occurred after two or more consecutive missing tumor assessments. Censoring rules for PFS follow the RECIST 1.1 guidelines and details can be found in Section 2.6.1.1.2.

2.6.1.1.2 Censoring pattern

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 2-6 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 LATA 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 2-6 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 LATA.

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 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 2-7 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	54

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 32 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 40 weeks but within 48 weeks from randomization (the matched scheduled tumor assessment is C11D1). For example, D1=8+2=10 weeks and D2=8+12+2=22 weeks.

Rule 3: if LATA happens after 48 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:

- '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 LATA 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.

2.6.1.2 Overall response rate

Overall response rate (ORR) is defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) as per local review. ORR will be evaluated according to RECIST 1.1. ORR based on RECIST 1.1 will be calculated based on the FAS and according to the ITT principle. ORR and its two-sided 95% exact CI (Clopper 1934) will be presented by treatment group. In addition, ORR in the subset of patient with measurable disease at baseline will be presented. Waterfall plot will also be generated (Section 2.6.1.3).

If the primary endpoint is statistically significant, ORR per RECIST 1.1 will be tested using Cochran–Mantel–Haenszel chi-square test method at a one-sided 2.5% significance level.

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".

2.6.1.3 Disease control rate (DCR)

DCR is defined as the proportion of patients with BOR of CR, PR, or SD or Non-CR/Non-PD.

DCR will be evaluated according to RECIST 1.1. DCR based on RECIST 1.1 will be calculated based on the FAS and according to the ITT principle. DCR and its two-sided 95% exact CI (Clopper 1934) will be presented by treatment group.

2.6.1.4 Time to response (TTR)

TTR is defined as duration of time between the date of randomization and the date of first documented response of either CR or PR, which must be subsequently confirmed (although date of initial response is used, not date of confirmation).

TTR will be evaluated according to RECIST 1.1.

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 LATA for patients without a PFS event. TTR will be summarized by treatment group based on RECIST 1.1. The distribution function of TTR will be estimated using the KM method. The median TTR along with two-sided 95% CIs will be presented by treatment arm.

2.6.1.5 Duration of response (DOR)

DOR is defined as the duration of time between the date of first documented response (CR or PR) and the date of first documented progression or death due to any cause.

DOR only applies to patients whose best overall response is CR or PR based on tumor response data per local review. If a patient has not had an event, DOR is censored at the date of LATA. Patients who never achieved a BOR of CR or PR will be excluded from the analysis. The distribution function of DOR will be estimated using the KM method. The median DOR along with two-sided 95% CIs will be presented by treatment arm.

2.6.1.6 Duration of follow-up

Study follow-up will be summarized using the following methods:

Summary of duration between randomization and cut-off date, and follow-up times for OS and PFS, which are defined as follows:

- Duration between randomization and data cut-off date = (Cut-off date – Date of randomization + 1) / 30.4375 (months). This item will be summarized overall.
- Follow-up time for OS = (Date of event or censoring – Date of randomization + 1) / 30.4375 (months) regardless of censoring. Date of censoring is defined as last contact date for OS. This item will be summarized by treatment arm.
- Follow-up time for PFS = (Date of event or censoring – Date of randomization + 1) / 30.4375 (months). Date of censoring is defined as LATA for PFS if no PFS event is observed. Date of disease progression or death will be used if patient has a PFS event. This item will be summarized by treatment arm.

All summaries will be reported in months.

In addition, median time to censoring will be computed by reversing censoring variable and performing KM analysis (Schemper 1996).

2.6.2 Safety run-in Part

BOR, ORR, DCR, PFS by Investigator's assessment per RECIST 1.1 and OS will be evaluated and summarized by dose cohort.

2.6.3 Analyses of secondary objective: Safety analyses

Safety set will be used for all safety analyses.

2.6.4 Randomized part

2.6.4.1 Adverse events (AEs)

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

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary SOC and for each PT using MedDRA coding by treatment arm. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades (version 5.0) 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 'All subject' column.

The following AE summaries will be produced by treatment arm:

- overview of AEs and deaths,
- AEs by SOC and PT,
- AEs by PT summarized by relationship,
- SAEs by PT summarized by relationship ,
- AEs leading to study drug discontinuation by PT,
- AEs leading to dose interruption by PT,
- AEs leading to dose change by PT,
- AEs leading to fatal outcome and by relationship

In addition, a summary of serious and non-serious AEs 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).

2.6.4.2 AEs of special interest / grouping of AEs

Data analysis of Adverse events of Special Interest (AESIs)

An AESI is a grouping of AEs that are of scientific and medical concern specific to compound NIS793. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs. Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A 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. The groups are defined according to the MedDRA terms defined in the program Case Retrieval Strategy (CRS) document and will be summarized. The latest version of the CRS document available at the time of the analyses will be used. For

each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided by treatment arm, (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 PT used to define each AESI will be generated.

2.6.4.3 Deaths

Separate summaries for on-treatment and all deaths will be produced by treatment arm, SOC and PT.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened patients.

2.6.4.4 Laboratory data

The summaries will include all assessments available for the lab parameter collected no later than 90 days after the last study treatment administration date (Section 2.1.2.3). Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for AEs (CTCAE) version 5.0.

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

- Shift tables using CTC grades to compare baseline to the worst on-treatment value (hypo and hyper worst grade will be summarized separately if applicable)
- 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 assessment closest to the planned date will be used. If two assessments are obtained with the same time difference compared to the scheduled visit day, the worst assessment will be used (worst either based on CTC grade or normal range). If there are multiple assessments as baseline candidate, the same baseline rule, as specified in Section 2.1.2.7 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	On or before Study Day 1[a]	≤ Study Day 1
C1D1	Study Day 1	Study Days 1 to 4
C1D8	Study Day 8	Study Days 5 to 11
C1D15	Study Day 15	Study Days 12 to 18
C2D1	Study Day 29	Study Days 19 to 32

C2D8	Study Day 36	Study Days 33 to 39
C2D15	Study Day 43	Study Days 40 to 46
C3D1	Study Day 57	Study Days 47 to 60
.....	.....	.....
Cycle k (with k = 4, 5…)	Study Day 28*(k-1)+1	Study Day 28*(k-1)-13 to 28*(k-1)+14 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

[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

Liver function parameters

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

The following summaries will be produced:

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

- TBL > 2xULN
- TBL > 3xULN

Combined elevations post-baseline:

For AST and ALT ≤ ULN at baseline

- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP ≥ 2xULN

For ALT or AST > ULN at baseline

- Elevated ALT or AST (*) & TBL (> 2x Bsl and 2xULN)
- Elevated ALT or AST (*) & TBL (> 2x Bsl and 2xULN) & ALP < 2xULN
- Elevated ALT or AST (*) & TBL (> 2x Bsl and 2xULN) & ALP ≥ 2xULN

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

2.6.4.5 Other safety data

2.6.4.5.1 ECG

ECG abnormalities for baseline and any post baseline assessments will be summarized by treatment arm. The clinically notable criteria will be described in the TFLs.

2.6.4.5.2 Vital signs and body weight

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

Data handling

Vital signs collected on treatment will be summarized.

Data analysis

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

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
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 (°C)	>= 39.1	-

The number and percentage of patients with notable vital sign values (high/low) will be presented by treatment arm.

2.6.5 Safety run-in part

Summaries of DLTs, AEs, SAEs, treatment related AEs, on-treatment deaths, AESI overview, Lab shift table based on key hematologic and biochemistry terms and Liver transaminase abnormality will be summarized. In addition, serious and non-serious AEs 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 listings specified for AE and death in Section 2.7.1 will be generated as applicable.

2.7 Analyses of secondary objective: Pharmacokinetic endpoints

Post implementation of protocol amendment 3, PK samples will no longer be collected.

2.7.1 PK analysis in Safety run-in part

PK summary statistics (arithmetic mean, geometric mean, SD, arithmetic CV, geometric CV, median, minimum and maximum) will be presented by treatment and visit/sampling timepoints. Concentrations below the lower limit of quantification (LLOQ) will be treated as zero in summary statistics.

2.7.2 PK analysis in Randomized part

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 NIS793 concentration will be presented at each scheduled time point.

PK parameters

CCI [redacted] in the randomized part, the descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) will be presented by treatment for PK parameters (as in Table 2-10) except Tmax, where only n, median, minimum and maximum will be presented.

CCI [redacted] and global patients, for which patients only sparse PK samples are planned to be collected, the descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) will be presented by treatment for Cmax, Ctrough and Ctroughss at appropriate timepoints in the same table (the column headers of the table will differentiate CCI [redacted]

The PK parameters in the Table 2-10 will be estimated and reported, when applicable. PK parameters will be derived based on the non-compartmental methods, when derivation of selective PK parameters is feasible, using Phoenix WinNonlin® software version 6.4.

Table 2-10 Non-compartmental pharmacokinetic analysis

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma or serum drug concentration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma or serum drug concentration (time)
Ctrough	The lowest serum/plasma drug concentration reached by a drug before the next dose is administered (mass x volume-1)

Handling of PK data below LLOQ or missing

All concentration values below the LLOQ are set to zero by the Bioanalyst. 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.

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

Population pharmacokinetic analysis

In this analysis, the CCI [redacted] data from safety run-in and randomized parts will be pooled. If there are adequate amount of data, a mixed-effects model may be applied to the serum NIS793 concentration-time data from this study along with other studies to generate post-hoc estimates of pharmacokinetic parameters using NONMEM to characterize NIS793 exposure and to determine the effects of intrinsic (i.e. demographic factors) and extrinsic covariates (e.g. concomitant medications, formulation) on NIS793 exposure. If there are sufficient data for analysis, the details of the population pharmacokinetic analyses may be provided in a separate reporting and analysis plan, and the results may be reported in a separate population pharmacokinetic report.

2.8 Analyses of secondary objective: Immunogenicity analyses

To evaluate the immunogenicity (IG) of NIS793 in combination with gemcitabine and nab-paclitaxel, incidence of anti-NIS793 anti-body by treatment arms for the randomized part will be summarized and presented.

2.8.1.1 Sample ADA status

Each IG sample is assessed in a three tiered 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 identified as positive in the confirmatory assay are considered ADA positive. 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: ADA positive (yes) or ADA negative (no)
- Titer (for positive samples): numerical representation of the magnitude of ADA response
- Drug tolerance level: highest drug concentration that does not interfere in the ADA detection method

Sample ADA status is determined based on the following definitions:

- *ADA-inconclusive sample*: Sample where assay is ADA negative and corresponding NIS793 PK concentration at the time of IG sample collection is greater than or equal to the drug tolerance level or missing.
- *Unevaluable sample*: Sample where assay is not available.
- *Determinant sample:* Sample that is neither ADA-inconclusive nor unevaluable.

The following definitions apply only to determinant samples:

  - *ADA-negative sample*: Determinant sample where assay is ADA negative and corresponding NIS793 PK concentration at the time of IG sample collection is less than the drug tolerance level.
  - *ADA-positive sample*: Determinant sample where assay is ADA 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.

Patient ADA status is defined as follows:

- *Treatment-induced ADA-positive patient*: patient with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample.
- *Treatment-boosted ADA-positive patient:* patient with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample.
- *Treatment-unaffected ADA-positive patient*: patient 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 patient*: patient with ADA-positive sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *ADA-negative patient*: patient with ADA-negative sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *Inconclusive patient*: patient who does not qualify as treatment-induced ADA-positive, treatment-reduced ADA-positive, treatment-boosted ADA-positive, treatment-unaffected ADA-positive, treatment-reduced ADA-positive, or ADA-negative.

The following summaries of ADA patient status (n and %) may be provided using Immunogenicity incidence set:

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

2.9 CCI

CCI

2.10 CCI

2.10.1 CCI

CCI

2.10.2 CCI

CCI

2.10.3 CCI

CCI

2.10.4 CCI

CCI

2.11 CCI

CCI

CCI

CCI

3 CCI

CCI

CCI

Table 3-1 CCI

CCI

CCI

CCI

Table 3-2 CCI

CCI

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study treatment

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Use the study treatment start date

For patients with missing study treatment start dates, no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Missing Element	Rule
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	**Rule** (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

The same rules described in Table 5-1 and Table 5-2 will be used for missing dates in the Diagnosis and Extend of Cancer domain. If the treatment start date is also missing for patients who did not manage to receive any treatment, then the randomization date will be used instead.

5.1.2.1 Handling missing month/day in date of death/last known patient alive from survival eCRF page

For rare cases when either day is missing or both month and day are missing for the date of death/last known patient alive from survival eCRF page, the follow imputation rules will be implemented:

- If only day is missing, then impute max [(1 mmm-yyyy), any valid date from database used for deriving last contact date +1].
- If both day and month are missing, then impute max [(1 Jan-yyyy, any valid date from database used for deriving last contact date +1].

5.1.2.2 Data handling for missing date of last administration

The following rule should be used for the imputation of date of last administration (please refer to Section 2.1.2.3) for a given study treatment component:

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The date of last administration is completely missing, and the EOT visit date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT visit:

Use last day of the Month (mm).

After imputation, compare the imputed date with the start date of that specific record, if the imputed date is < start date of that record Use the start date of that record.

Patients with missing start dates are to be considered missing for all study treatment component related calculations described in Section 2.4.1.1 and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.2.3 Other imputations

Not applicable

5.2 AEs coding/grading

AEs are coded using the MedDRA terminology (version 27.0 or higher).

AEs will be assessed according to the CTCAE version 5.0

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE version 5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for an xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

5.4 Statistical models

5.4.1 Primary analysis

Analysis of time to events Data

Hypothesis and test statistic

The null hypothesis stating that OS survival distributions of the two treatment arms are equivalent will be tested against one-sided alternative.

H_{01} (null hypotheses): $\Theta_1 \geq 1$ vs. H_{a1} (alternative hypotheses): $\Theta_1 < 1$

Where Θ_1 is the log HR of OS in the NIS793 (investigational) in combination with gemcitabine and nab-paclitaxel vs. placebo (control) in combination with gemcitabine and nab-paclitaxel. Log-rank test will be used to test the difference between the treatment arms. The LIFETEST procedure in SAS with the TIME statement including a variable with survival times and a (right) censoring variable, and with STRATA statement including variables of stratification factors and with GROUP option under STRATA statement. As an output of the procedure, the rank statistic S and variance var(S) will be obtained. Under the null hypothesis, the test statistic $Z=S/\sqrt{[var(S)]}$ is approximately normally distributed. The one-sided p-value will be obtained from normally distributed Z statistic.

One-sided will be obtained using Z statistic.

KM estimates

An estimate of the survival function in each treatment arm will be constructed using KM (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment arm will be obtained along with two-sided 95% CIs calculated from PROC LIFETEST output using the method of (Brookmeyer and Crowley 1982). KM estimates of the survival function with two-sided 95% CIs at specific time points will be summarized. The standard error of the KM estimate will be calculated using Greenwood's formula (Collett 1994).

Hazard ratio (HR)

HR will be estimated by fitting the Cox proportional hazards model using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

A stratified unadjusted Cox model will be, i.e. the MODEL statement will include the treatment arm variable as the only covariate and the STRATA statement will include stratification variable(s).

HR with two-sided 95% CI will be based on Wald test.

Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

Checking proportionality of hazard assumption

Plots (SURVIVAL LOGSURV LOGLOGS) generated by LIFETEST procedure in SAS will be used to provide visual checks of the proportional hazard assumption.

LOGLOGS plots log (cumulative hazard)

The LOGLOG plot will show parallel curves if hazards are proportional.

Time to first tumor assessment

In order to investigate whether there are systematic differences between treatment arms in the timing of the first tumor assessment (TA), an exploratory analysis of time to first TA will be performed. This analysis will be performed for the local radiology assessments only. Distinct TAs are identified based on the visit name. If the TAs within one evaluation are done over more than one day, the date of TA will be the first day. Time to 1st TA will be calculated from randomization (date of 1st TA - date of randomization + 1), i.e. only post-randomization TAs will be considered. The identification of the first TA will be based on the calendar dates.

TAs done after documented disease progression or after the analysis cut-off date will be excluded. Patients with no TA will be censored at the date of last contact.

Ascending KM curves will be constructed by treatment arm. KM medians with two-sided 95% CIs will be presented. The following will be summarized by treatment arm: number of patients with a first TA, number of patients censored.

Time to second tumor assessment

As above, this analysis will be performed for the local radiology assessments only. This exploratory analysis will include all patients from the FAS who have a 1st TA corresponding to an overall lesion response different from disease progression. Distinct TAs are identified based on the visit name. If the TAs within one evaluation are done over more than one day, the date of TA will be the first day. Time to second TA will be calculated from randomization (date of second TA - date of randomization + 1), i.e. only post-randomization TAs will be considered. TAs done after disease progression or after the analysis cut-off date will be excluded. Patients with no second TA will be censored at the date of last contact.

Ascending KM curves will be constructed by treatment arm. KM medians with two-sided 95% CIs will be presented. The following will be summarized by treatment arm: number of patients with second TA, number of censored.

If one of the analyses (time to 1st TA, time to second TA) or both show difference indicating potential bias between the treatment arms a sensitivity analysis will be performed to address the impact of the bias introduced by different timing.

6 Reference

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