**Official Title:** A Dose-optimization, Exploratory Phase Ib/II Study to Assess Safety and Efficacy of the Second Mitochondrial-derived Activator of Caspases (SMAC) Mimetic Debio 1143, When Given in Combination with the Anti-PD-1 Antibody Nivolumab in Patients With Specific Solid Tumors Who Have Progressed During or Immediately After Anti-PD-1/PD-L1 Treatment

**NCT Number:** NCT04122625

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# STATISTICAL ANALYSIS PLAN

## DEBIO 1143-106

SMARTPLUS-106: Debio 1143 a SMAC Mimetic in Combination with Nivolumab in Patients Failing Prior PD-1/PD-L1 Treatment: A Basket Trial

A dose-optimization, exploratory phase Ib/II study to assess safety and efficacy of the Second Mitochondrial-derived Activator of Caspases (SMAC) mimetic Debio 1143, when given in combination with the anti-PD-1 antibody nivolumab in patients with specific solid tumours who have progressed during or immediately after anti-PD-1/PD-L1 treatment

**AUTHOR:** [redacted]

**VERSION NUMBER AND DATE:** V5.0, 19APR2022

# STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan (SAP) v5.0 (dated 19APR2022) for protocol Debio 1143-106

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Upon review of this document, the undersigned approves this version of the SAP, authorizing that the content is acceptable for the reporting of this study.

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# MODIFICATION HISTORY

| Unique Identifier for this Version | Date of the Document Version | Author | Significant Changes from Previous Authorized Version |
|---|---|---|---|
| 1.0 | 05APR2019 | [redacted] | Not Applicable – First Version |
| 2.0 | 29OCT2019 | [redacted] | - Patient profiles and TLF shells now in separate documents<br>- Updates following Debiopharm review of the list of TLFs and corresponding shells<br>- Updates to be in line with protocol version 3 |
| 3.0 | 17NOV2020 | [redacted] | Section 5.5 Added for the extended period after the protocvol amendment 3<br>Section 6.5 Efficacy Analysis Set:<br>- treatment failure definition updated to take into account Covid-19 impact<br>- Add details on the criteria for the definition of Efficacy population ( 7 categories)<br>Section 10.1 Subject Disposition:<br>categories added in the summary table<br>Section 13 Prior Anti-Cancer Treatments:<br>added a listing for prior and current anti-cancer treatments<br>Section 16.1 Derivation:<br>Planned cumulative dose definition has been updated<br>Section 17.2.1.5 Progression-free survival (PFS): censoring rules more detailed, adding death due to COVID-19.<br>Section 17.2.4 Sensitivity Analysis of Secondary Effiacy:<br>Variables Another sensitivity analysis will be performed by censoring the OS at the time of death due to COVID-19. |

| | | | |
|---|---|---|---|
| | | | Section 18.1.14 TEAEs leading to death: Additional listing added for all AEs leading to death |
| V4.0 | 29JUL21 | [redacted] | Formula for derivation of Duration of exposure updated in section 15.1.<br>Compliance derivations updated in section 16.<br>Mention that Efficacy population is not applicable for Part A in section 6.5.<br>Update the wording of "Critical deviations" by "Major deviations" In section 10.2.<br>Update the definition of Medical History in section 12.<br>Mention in section 4.3 that no pooling of part A and Part B will be performed. |
| V5.0 | 19APR2022 | [redacted] | Section 6 Analysis Set:<br>- Clarify that efficacy analysis set is a subset of ITT<br>- Clarify that RP2D is not applicable for Part B<br>- Clarify that any patient with one of the deviation described in category 5 will be automatically excluded from Efficacy population<br>- Clarify that category 7 corresponds to patients whose treatment had to be delayed or interrupted for reasons related to COVID-19 pandemic only and did not receive at least 25% of the planned Debio1143 dose or didn't receive any dose of nivolumab infusion during cycle 1<br><br>Section 7.6 Statistical Test: |

| | | | |
|---|---|---|---|
| | | | - Update the rounding rules for quantitative summaries, to not have irrelevant decimales<br><br>Section 14 Medications<br>- Update the definition of Concomitant medications<br><br>Section 18.1.15 Most common TEAE<br>- Clarify that AEs where the overall percentage is ≥ 5% will also be summarized by SOC and PT<br><br>Section 18.5.1 Vital Signs Markedly Abnormal Criteria<br>- Low and High Markedly Abnormal Criteria updated for Weight<br><br>Section 20 Pharmacodynamics<br>- Update the definition of On-treatment period<br><br>Typo corrected throughout all the document |

# TABLE OF CONTENTS

# 1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, pharmacokinetic (PK), pharmacodynamic (PDy), and genetic data for Protocol Debio 1143-106. It describes the data to be summarized and analysed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 4 dated 03rd April 2020. This SAP will cover analyses for both part A (phase 1b) and part B (phase 2).

# 2. STUDY OBJECTIVES

## 2.1. PRIMARY OBJECTIVE

### 2.1.1. PART A

The primary objective of the dose-optimization part of the study is to determine the recommended phase 2 dose (RP2D) taking into account dose limiting toxicities (DLTs) in Cycle 1, overall safety/tolerability and PK, by optimizing doses of Debio 1143 when combined with the standard dose of nivolumab, as well as treatment compliance in patients with advanced solid malignancies who failed prior systemic standard treatments.

### 2.1.2. PART B

The primary objective of the basket trial is to evaluate the preliminary anti-tumour activity of Debio 1143 at the RP2D in combination with nivolumab at the standard dose, overall and in each patient cohort.

## 2.2. SECONDARY OBJECTIVES

### 2.2.1. PART A

For the dose-optimization part, secondary objectives are to assess the:

1. PK disposition of Debio 1143 (including its metabolite Debio 1143-MET1) and nivolumab when administered in combination.
2. Anti-tumour activity of Debio 1143 in combination with nivolumab in patients with advanced solid malignancies.

### 2.2.2. PART B

For the basket trial, secondary objectives are to assess the:

1. Safety and tolerability of the RP2D of Debio 1143 when given in combination with nivolumab in patients with advanced solid malignancies.
2. PK disposition of Debio 1143 (and its metabolite Debio 1143-MET1) and nivolumab when administered in combination.

## 2.3. EXPLORATORY OBJECTIVES

The exploratory objectives of this study are:

1. To explore potential predictive and PDy biomarkers of Debio 1143 and nivolumab when administered in combination, in blood and tumour tissue, [redacted]
2. To explore genetic variations in drug metabolism enzyme and transporter (DMET) genes associated with differences in the PK disposition of Debio 1143 in combination with nivolumab
3. To explore the exposure/response relationship for efficacy and safety (including PK/PDy correlations, if applicable) of Debio 1143 in combination with nivolumab
4. To explore correlations between response, clinical parameters, immune correlates, and putative biomarkers, [redacted]
5. To explore the relationship between Debio 1143 plasma concentrations and QTcF

# 3. STUDY ENDPOINTS

## 3.1. PRIMARY ENDPOINTS

### 3.1.1. PART A

The primary endpoint of part A is the RP2D of Debio 1143 when combined with the standard dose of nivolumab, in patients with advanced solid malignancies who received prior systemic standard treatment and failed a prior PD-1/PD-L1-containing treatment, as per DLT occurrence in less than one-third of evaluable treated patients at the RP2D dose level.

### 3.1.2. PART B

The primary endpoint of part B is the confirmed objective response rate (ORR) as per Response Evaluation Criteria in Solid Tumor (RECIST) v1.1 and/or Gynecologic Cancer Intergroup (GCIG) criteria (Cohort 4, if applicable).

## 3.2. SECONDARY ENDPOINTS

Secondary endpoints for both study parts (unless otherwise specified) are:

- Incidence and severity of treatment-emergent adverse events (TEAEs) and clinical laboratory abnormalities, according to National Cancer Institute-Common Terminology Criteria for Adverse Events NCI-CTCAE version 5.0 criteria
- Changes in vital signs: systolic/diastolic blood pressure, heart rate (both after at least 5 minutes of supine rest), temperature, and weight; electrocardiogram (ECG) and Eastern Cooperative Oncology Group Performance Status (ECOG-PS)
- Incidence of premature treatment discontinuations and treatment modifications due to TEAEs and laboratory abnormalities (i.e., treatment compliance)
- Tumor response determined according to RECIST v1.1 and/or GCIG criteria (Cohort 4, if applicable):
    - Confirmed (Part A) and unconfirmed (Parts A and B) ORR
    - Disease control rate (DCR), defined as any response, partial or complete (PR or CR) + stable disease (SD)
    - Time-related endpoints as median time to response, median duration of response (DOR), median progression-free survival (PFS), PFS rate every months, median overall survival (OS), OS rate at 12 months and 18 months (if data allow)
- PK parameters of Debio 1143 and Debio 1143-MET1 as defined in the available population PK disposition model and, if appropriate, post-hoc estimates of areas under the curve (AUCs), Cmax, and Cmin; serum concentration versus time profiles of nivolumab and, if deemed appropriate, relevant nivolumab PK parameters derived from a population PK model.

## 3.3. EXPLORATORY ENDPOINTS

Exploratory endpoints are:

- Potential predictive (*) and PDy biomarkers of Debio 1143 combined with nivolumab, in blood and tumor tissue [redacted]
- Best overall response (BOR) evaluation using the novel iRECIST 2017 guideline for immunotherapeutics
- Correlations between PK disposition of Debio 1143 combined with nivolumab and clinical response and/or any tumor metrics

- Correlations between PK disposition of Debio 1143 combined with nivolumab and safety profile, and PDy if applicable
- Correlations between Debio 1143 and Debio 1143-MET1 plasma concentrations and changes from baseline in QTc interval as corrected by Fridericia (QTcF).
- Correlations between response, clinical parameters, immune correlates and putative biomarkers, [redacted]
- Genetic variations in DMET genes associated with differences in the PK disposition of Debio 1143 in combination with nivolumab (*).

(*) – the analysis of these endpoints will be described in a separate analysis plan.

# 4. STUDY DESIGN

## 4.1. GENERAL DESCRIPTION

### 4.1.1. PART A

Part A has an open-label, multicentre dose-optimization design applying the classical 3+3 method, aiming at optimizing the Debio 1143 dose in combination with standard doses of nivolumab (OPDIVO®) to determine the RP2D taking into account safety/tolerability and PK, as well as the treatment compliance in pre-treated patients with advanced solid malignancies.

Eligible patients will enter Part A of the study in cohorts of three evaluable patients. The starting dose of Debio 1143 will be 150 mg, daily, administered orally for 10 consecutive days every 2 weeks (i.e., Days 1-10 and Days 15-24 inclusively of each 28-day cycle [q4w]). The dose will be optimized according to the observed DLTs, patient treatment compliance, safety/tolerability and PK data, if applicable.

The DLT period is defined as Cycle 1 (i.e. lasting 4 weeks or longer in case of dosing delays). Treatment-related toxicities fulfilling DLT criteria but occurring after Cycle 1 (i.e., delayed DLTs) may also be considered for RP2D definition after discussion and agreement between the Investigators, Data Safety Monitoring Committee (DSMC) and the sponsor.

Nivolumab will be administered at 240 mg (flat dose) over at least 30 minutes as an IV infusion on Days 1 and 15 of a 28-day cycle. From Cycle 3, patients may be switched to nivolumab at a dose of 480 mg IV over at least 60 minutes on Day 1 q4w, exclusively upon Investigator request with the Sponsor agreement.

The maximum explored Debio 1143 dose will be 200 mg/day. Neither Debio 1143 dose escalation beyond this threshold nor any nivolumab dose increases are foreseen in this study. In individual cases of severe toxicity, the Debio 1143 dose may be reduced by a maximum of two decrements of 50 mg/day or up to a minimum dose of 100 mg/day.

According to the 3+3 dose-optimization design, if none of the three evaluable patients at the starting dose cohort experiences a DLT during Cycle 1, three more patients will be treated at the next dose level. However, if one of the first 3 evaluable patients experiences a DLT during the DLT period, 3 more patients will be treated at the same dose level. If ≤ 1 out of 6 evaluable patients experiences a DLT during the first cycle, at the starting dose level, then dose escalation will proceed to the second dose level. If ≥ 2 DLTs are observed during the first cycle among the 3 or 6 evaluable patients treated with the initial dose level, then recruitment will be stopped temporarily or definitively until the reasons for this finding have been clarified. If the dose is increased to the second dose level, 3 to 6 evaluable patients will be included, and the 3+3 design rules will be applied again. If ≤ 1 out of 6 evaluable patients experience a DLT during the DLT period at the second dose level, this dose will be considered as the optimal dose level i.e., the RP2D. If ≥ 2 evaluable patients experience a DLT during the DLT period at the second dose level, the initial dose level will then be declared the RP2D. Once the RP2D is defined, any patient still receiving treatment can be switched to the RP2D, if deemed appropriate by the Investigator and agreed by the sponsor.

The sample size will be determined by the number of patients included per dose level and the observed toxicities. Given that (i) a maximum number of two dose levels will be explored, (ii) a classical 3+3 design will be used and (iii) at least 6 patients need to be treated at the RP2D before the phase II part starts formally, between 3-12 evaluable patients will be included. Patients non-evaluable for DLT will be replaced as appropriate.

### 4.1.2. PART B

Part B is a multicenter, open-label, basket trial using Debio 1143 in combination with nivolumab at the RP2D as previously defined in Part A, in patients with advanced/unresectable solid tumours. Eligible patients will be simultaneously included into four cohorts according to tumour type:

- Cohort 1: Small cell lung cancer (SCLC; including extrapulmonary small-cell carcinomas or large cell neuroendocrine lung carcinoma, as per World Health Organisation [WHO] Classification of Lung Tumors of 2015)
- Cohort 2: Squamous Cell Carcinoma of the Head and Neck (SCCHN; nasopharyngeal carcinomas are excluded)
- Cohort 3: Gastrointestinal (GI) cancers, including oesophageal, gastric, colorectal or pancreatobiliary tumours, with known microsatellite instability-high (MSI-H)/ mismatch repair deficiency (MMRd) or other known deoxyribonucleic acid (DNA) damage response (DDR) abnormalities (incl. homologous

recombination deficiency [HRD]).

- Cohort 4: platinum-resistant epithelial ovarian cancer (EOC), endometrial cancer, primary peritoneal cancer (PPC) and cervical cancer, with known MSI-H/MMRd, hereditary/somatic mutations of the breast cancer type 1 (BRCA1) and BRCA type 2 (BRCA2) genes or other known DDR abnormalities (incl. HRD).

The primary objective of Part B is to assess whether the combination of Debio 1143 with nivolumab is active overall and in each cohort. Early futility stopping rules based on ORR (unconfirmed) will be used. In each cohort, if no unconfirmed response is observed according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) or Gynecologic Cancer Intergroup (GCIG) criteria (Cohort 4, if applicable) once the initial 8 evaluable patients have been assessed at least twice after baseline or have discontinued their treatment earlier, futility will be concluded and recruitment will be stopped in that cohort. If at least one response (unconfirmed) is documented in the initial 8 evaluable patients, recruitment shall continue up to 11 evaluable patients. At least two unconfirmed responses must then be observed in these 11 evaluable patients to continue the recruitment up to 15 evaluable patients in that cohort.

The total sample size will be between 32 (if all cohorts are futile) and 60 evaluable patients (if none of the 4 cohorts is futile). If a patient is not evaluable (i.e. not included in efficacy analysis set) he/she will be replaced.

In Part B, patients will receive Debio 1143 at the RP2D established in Part A, in combination with nivolumab at the standard dose. Per-patient dose adjustments of Debio 1143 will be considered according to the severity of any eventual observed toxicity.

Participants are planned to be treated with Debio 1143 and nivolumab for up to 52 weeks (i.e., 13 cycles, until any of the following events occurs: symptomatic progressive disease (PD), asymptomatic but confirmed PD (as per iRECIST), unacceptable toxicity (per Investigator judgment and despite up to two dose adjustments), patient withdrawal, or treatment delay greater than 4 and 8 weeks (+1 week tolerance) for Debio 1143 and nivolumab, respectively.

Permission to prolong the study treatment for one additional year can be exceptionally granted by the Sponsor, if patients are deriving continuous clinical benefit from the study treatment. Medical justification for extending the treatment and the assessment of the risk/benefit balance must be provided by the Study Investigator and will be discussed with the Sponsor. The decision to further extend study treatment will be re-evaluated on a yearly basis for each patient.

## 4.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 8.3.1 of the protocol.

## 4.3. CHANGES TO ANALYSIS FROM PROTOCOL

Screened Analysis Set

The protocol does not mention a screened analysis set but it has been included in this SAP for the purposes of subject disposition analyses.

Analysis of primary endpoint (ORR)

The protocol mentions reporting ORR at final analysis in terms of relative and absolute frequencies along with a 95% confidence interval. As this is a Bayesian analysis, we need to provide an estimate of the ORR based on the posterior beta distribution along with a 95% credibility interval. This has been described in section 17.1.3.

Pharmacokinetics

Graphical presentation of concentration-time profiles is simplified to depict geometric mean concentrations ± geometric standard deviations and individual profiles on log10/linear scales.

For the non-compartmental PK analysis, in addition to the analysis for plasma Debio 1143 and Debio 1143-MET1 described in the protocol, PK parameters will also be calculated for serum nivolumab.

Additional descriptive statistics, in addition to the ones specified in the protocol, are included for concentration and PK parameter summaries for consistency with data presentation in previous study. For the list of all descriptive statistics, refer to section 7.6.

Efficacy Analysis Set

As per protocol, treatment failure is defined as any of the following: death, unacceptable toxicity, clinical deterioration and/or symptoms worsening. Treatment failure definition is updated and defined as any: death, unacceptable toxicity, clinical deterioration and/or symptoms worsening, ***except those linked to COVID-19***.

The following category is not described in the protocol:

Category 7: Patients whose treatment had to be delayed or interrupted for reasons related to COVID-19 pandemic only and did not receive at least 25% of the planned Debio1143 dose or skipped one nivolumab infusion during cycle 1. Exposure during the first 3 treatment cycles will also be considered as part of the assessment of patients who fall into this category.Planned analysis

Due to the futility of the part B cohorts, no pooling of part A and Part B will be performed.

Another sensitivity analysis will be performed by censoring the OS at the time of death due to COVID-19, which was not planned as per protocol. This will be applicable only if there is at least one death due to COVID-19.

# 5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses to be used for dose escalation decisions (Part A)
- Analyses for DSMC meetings (Part A and B)
- Futility monitoring (Part B)
- Final analysis for the Main study period
- Final anlaysis for the Extended study period

## 5.1. DOSE ESCALATION DECISIONS (PART A)

After each 3 or 6 evaluable patients, the DLTs in cycle 1 will be assessed and a decision on the next dose will be made following the classic 3+3 design (refer to Section 4.1.2).

To support this, patient profiles, based on raw data, will be produced including the following information:

- DLTs
- Patient evaluability
- Demographic characteristics
- Tumour type and cancer history
- Medical history
- Previous anti-cancer therapies
- Debio 1143 exposure & modifications
- Nivolumab exposure & modifications
- AEs, serious adverse events (SAEs), and adverse events of special interest (AESIs)
- Prior and concomitant medications
- Lab parameters
- Screening laboratory assessments
- Endocrinology
- All efficacy data including target, non-target and new lesions. Also, response as assessed by RECIST/GCIG will be presented
- Vital signs
- ECOG performance status

- Treatment/study withdrawal information
- Deaths

In addition, a table summarising the subject disposition will be provided with the patient profiles.

The templates for the patient profiles are provided in a separate document: Debio 1143-106 Patient Profile Shells FINAL.

## 5.2. DATA SAFETY / EFFICACY MONITORING COMMITTEE (DSMC)

A DSMC will overview study conduct during both parts A and B. It will be composed of at least all actively involved investigators (or their designee), the Sponsor Medical Director and the Contract Research Organization (CRO) medical monitor as voting members, and will meet regularly to overview the clinical safety of the patients, laboratory data and the conduct of the study. Ad hoc members may be invited as needed. The full details regarding the composition of the DSMC and the timing of analyses will be included in the DSMC charter.

For part A, only the patient profiles as described in section 5.1 will be produced for DSMCs. For part B, TLFs will be produced once there are at least 4 patients enrolled in each cohort or at least 15 patients overall, whichever occurs first. Until then, only the patient profiles as described in section 5.1 will be produced. The TLFs to be produced for DSMC analyses will be indicated in the Debio 1143-106 TLF Shells FINAL document and the DSMC charter.

## 5.3. FUTLITY MONITORING ANALYSES

There will be two futility monitoring analyses in each cohort. The cut-off for futility analyses is defined as the time when the last ongoing patient from the first 8/11 evaluable patients has at least 2 post-baseline tumor assessments or prematurely discontinued.

No formal interim analysis will be performed during the futility monitoring. Only the number of evaluable patients with, at least, unconfirmed responses as per RECIST v1.1 and/or GCIG criteria (if applicable) will be checked vs. the futility boundaries in each cohort independently.

Bayesian posterior probability of the unconfirmed objective rate will be used for the early stopping rules for futility.

A general confirmed response rate of 15% is considered as promising, justifying further development. This corresponds to approximatively 17% unconfirmed response rate. On the other hand, 5% is considered to be the general futility response rate (unconfirmed).

Assuming a probability confidence threshold for futility stopping of 20%, and a maximum sample size of 15 evaluable patients by cohort, the futility stopping boundaries are defined for each cohort as follows:

- 0 unconfirmed response out of 8 evaluable patients for the first futility monitoring analysis and
- ≤1 unconfirmed response out of 11 evaluable patients for the second futility monitoring analysis

Consequently, if no unconfirmed objective response is documented as per RECIST v1.1 and/or GCIG criteria (if applicable) after the 8th evaluable patient is assessed, futility will then be concluded and the recruitment will be stopped in the corresponding cohort. In case at least one unconfirmed response is documented in the first 8 evaluable patients, recruitment shall continue up to 11 evaluable patients and a second futility monitoring analysis will be conducted. If at least two unconfirmed responses are documented in the first 11 evaluable patients, the recruitment will continue up to 15 evaluable patients; otherwise the recruitment will be stopped. The early stopping for futility is binding.

The Bayesian posterior probability will be used to preliminary assess the primary efficacy endpoint: the confirmed ORR as per RECIST v1.1 and/or GCIG criteria, if applicable. The unconfirmed ORR will be used for the early futility stopping rules.

The main metrics of the Bayesian efficacy monitoring via posterior probability are the following:

- Denote $\theta$ as the response rate. The prior distribution of $\theta$ is: $\theta \sim \text{Beta}(a0,b0)$
- Let $R$ be the number of responses in $n$ observations, $R \sim Binomial\ (\theta, n)$.
- The posterior distribution of $\theta$ given observed $r$ responses and $n-r$ no responses is:

  $\theta \mid r, n \sim \text{Beta}(a0+r,b0+n-r)$.

For futility monitoring, the following decision rules are introduced:

1. Early stopping for futility: let $\theta_{fut}$ be the reference response rate for futility monitoring and $P_{fut}$ be the probability confidence threshold for futility. The trial should be stopped early and the treatment is declared inefficacious if

   $Prob(\theta \leq \theta_{fut} \mid r, n) > P_{fut}$.

2. Criterion for declaring efficacy: let $\theta_{eff,final}$ be the reference response rate for declaring efficacy at the final stage, and $P_{eff}$, be the probability confidence threshold for final efficacy.

The treatment is declared efficacious at the end of the trial if

$$Prob(\theta > \theta_{eff,final} \mid r, n) \geq P_{eff,final}.$$

In this trial, the metrics are the following:

| Metric | Value |
|---|---|
| Reference response rate for futility monitoring ($\theta_{fut}$) | 0.05 |

| | |
|---|---|
| Probability confidence threshold for futility stopping ($P_{fut}$) | 0.2 |
| Reference response rate for efficacy ($\theta_{eff,final}$) | 0.15 for confirmed ORR and 0.17 for unconfirmed ORR |
| Probability confidence threshold for declaring efficacy ($P_{eff,final}$) | 0.8 |
| Prior distribution for theta: Beta ($a$0,b0) | (0.5, 0.5) |
| Maximum number of patients per cohort | 15 |

The futility boundaries are described in the table below:

| # Patients (inclusive) | # Responses (inclusive) to be considered as non-futile |
|---|---|
| 8, 9 & 10 | >= 1 |
| 11, 12, 13 & 14 | >= 2 |

The TLFs to be produced for the futility monitoring analyses (for all evaluable and non-evaluable patients) will be indicated in the Debio 1143-106 TLF Shells FINAL document and they will cover the following:

- Subject disposition
- Exclusion from analysis sets
- Demographics
- Baseline disease characteristics
- Study drug exposure (Debio 1143 and Nivolumab)
- Unconfirmed best overall response and unconfirmed objective response rate
- Swimmers plot including pevious anticancer therapies

## 5.4. FINAL ANALYSIS FOR THE MAIN STUDY PERIOD

All final, planned analyses identified in this SAP for the Main study period will be performed by IQVIA Biostatistics following Sponsor authorization of this SAP, Sponsor authorization of analysis sets, and Database Freeze .

The final analysis for the Main study period will include all study endpoints and will be performed within one year of the End of the Main study period i.e., 18 months after the last patient in (LPI) or 60 days after the last patient last visit (LPLV), whichever occurs first . The main study results will be presented separately for both study parts. Only data collected during the Main study period will be included in the final analysis of the Main study period.

## 5.5. FINAL ANALYSIS FOR THE EXTENDED STUDY PERIOD

Data collected after the Main study period for patients entering the Extended study period will be analysed using descriptive statistics and included in an addendum to the Final CSR. If only few patients or few visits are collected, data will be reported as individual listings.

# 6. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the final analysis of the Main study period.

## 6.1. SCREENED ANALYSIS SET

The screened (SCR) analysis set contains of all subjects who signed the informed consent form.

## 6.2. RP2D ANALYSIS SET (PART A ONLY)

Patients will be considered as not evaluable for DLTs and excluded from the RP2D analysis set, if they did not receive at least 70% of Debio 1143 (i.e. a maximum of 6 missed Debio 1143 doses is allowed) and at least one nivolumab dose as planned in cycle 1 for any reason other than DLT.

Patients not evaluable for DLT will be replaced if there are less than 3 evaluable patients by cohort.

If a treatment modification during the DLT period leads to a potentially non-evaluable patient, the final decision regarding the patient's evaluability will be taken only at the end of his/her DLT period. If the patient experiences a DLT, he/she will be considered as evaluable regardless of his/her exposure.

RP2D is not applicable for part B because TLFs will not be produced based on this analysis set for part B.

## 6.3. SAFETY ANALYSIS SET

The safety (SAF) analysis set will contain all patients who were enrolled and received at least one dose of any study drug.

## 6.4. INTENTION-TO-TREAT ANALYSIS SET

The intention-to-treat (ITT) analysis set will contain all enrolled patients who took at least one dose of any study drug.

## 6.5. EFFICACY ANALYSIS SET (PART B ONLY)

The efficacy (EFF) analysis set will contain all ITT patients who have:

- measurable disease according to RECIST v1.1 and/or GCIG criteria (Cohort 4, if applicable),
  and
- a baseline tumor assessment and at least one evaluable post-baseline tumor assessment, either CT or MRI for RECIST evaluable patients, or CA-125 dosage performed after baseline, if applicable,
  or
- treatment discontinuation occurred before any efficacy assessment was done due to treatment failure, defined as any: death, unacceptable toxicity, clinical deterioration and/or symptoms worsening, except those linked to COVID-19 (COVID-19 recorded as an AE in eCRF).

In order to assess these criteria, prior to each scheduled analysis where efficacy will be monitored, the study's statistician will present each of the below 7 category's data to the Debiopharm's Medical Director and IQVIA's Medical Monitor who will be tasked to adjudicate cases for exclusion from the efficacy population.

Category 1: Patients who did not have a baseline tumour assessment

a. based on imaging or

b. CA125 (where appropriate)

Category 2: Patients who did not have measurable disease according to

a. RECIST or

b. GCIC criteria (where applicable)

Category 3: Patients who did not have at least 1 post-baseline tumour assessment according to

a. RECIST or

b. GCIC criteria (where applicable)

If any of the above listed protocol deviations have been observed in categories 1 to 3, patients will be excluded from the efficacy population and will need to be "replaced".

Category 4: Patients who discontinued study treatment before the first post-baseline tumour assessment was performed due to treatment failure, except those linked to COVID-19 (COVID-19 recorded as an Adverse Event in eCRF), which include any of the following

a. Death

b. Unacceptable toxicity

c. Clinical deterioration and

d. Symptomatic worsening

Patients who failed treatment and included in category 4, will be kept in the efficacy population and will not be replaced

Category 5: Any critical deviations that may affect the risk benefit ratio

a. Cancer diagnosis (inclusion criteria 3 and 11)

b. Other malignancies (exclusion criterion 13)

c. Prior anti-cancer treatment (inclusion criteria 4, 5 and 6; exclusion criteria 2, 5, 6 an7)

d. Co-morbidities (exclusion criteria 4 and 10)

e. Inadequate hematologic, renal and hepatic function (inclusion criterion 9)

Category 6: Patients who used any of listed drugs prohibited on this protocol

Category 7: Patients whose treatment had to be delayed or interrupted for reasons related to COVID-19 pandemic only and did not receive at least 25% of the planned Debio1143 dose or didn't receive any dose of nivolumab infusion during cycle 1. Exposure during the first 3 treatment cycles will also be considered as part of the

assessment of patients who fall into this category.

Efficacy data assessed after any of these deviations have been observed in patients who are included in categories 5 through 7 will be excluded from the efficacy analysis. However, for category 6 and 7, this will not automatically lead to the exclusion of these patients from the efficacy population (any patient with one of the deviation described in category 5 will be automatically excluded from Efficacy population because these deviations are related to inclusion/exclusion criteria).

In case after the exclusion of efficacy data assessed after protocol violations described in categories 5 and 6 the patients will fulfil the criteria from category 1 or 3, the patients will be excluded from the efficacy analysis set.

Efficacy analysis set is not applicable for part A because TLFs will not be produced based on this analysis set for part A. For part B, in case no patient is excluded from efficacy analysis set (i.e. efficacy analysis set is equal to ITT analysis set), outputs on efficacy analysis set will not be produced.

# 7. GENERAL CONSIDERATIONS

## 7.1. REFERENCE START DATE AND STUDY DAY -

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of any study medication, (Day 1 is the day of the first dose of any study medication).

If the date of an event is on after the reference date, the following will be calculated:

- study day = date of event – reference date + 1
- cycle day = (date of an event – date of earliest administration of Nivolumab and/or Debio 1143 in Cycle n) + 1, where date of an event < date of earliest administration of Nivolumab and/or Debio 1143 in Cycle n

In listings, an assessment date will be supported by the cycle number/day which takes the format CxDy, where Cx is the cycle number as recorded in the study exposure (nivolumab) eCRF and Dy is the cycle day.

If the date of an event is prior to the reference date, then:

- Study Day = date of event – reference date

In the situation where the event date is partial or missing, study day, and any corresponding durations will not be calculated.

## 7.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first administration of study drug, it will be assumed that it was performed prior to study treatment administration (if time is not available).

## 7.3. DERIVED TIMEPOINTS

There will be no derived timepoints for by-visit analyses. The data will be presented by visit as recorded in the eCRF.

## 7.4. UNSCHEDULED VISITS

In general, for by-visit summaries, data recorded at the nominal visit will be presented (including early termination visit like “end of treatment” or “end of study”). Unscheduled measurements will not be included in by-visit summaries but will contribute to the best/ worst case value where required (e.g. shift table). Listings will include both scheduled and unscheduled data.

All tumour assessment and/or CA-125 data from both scheduled and unscheduled visits will be included in the analyses described in section 17 of this SAP.

## 7.5. WINDOWING CONVENTIONS

Regarding PK data, concentrations with actual sampling time outside the windows of tolerance specified in Table 8-5 of protocol will be only excluded from the PK analyses in case of pre-dose concentrations.

## 7.6. STATISTICAL TESTS

The default significant level will be 5%; confidence intervals (CIs) will be 95% and all tests/CIs will be two-sided,

unless otherwise specified in the description of the analyses.

Ordinal and continuous data will be presented in the form of descriptive statistics, as the number of observations, mean, standard deviation, minimum, 25$^{th}$ percentile (Q1), median, 75$^{th}$ percentile (Q3), maximum and two-sided 95% CI.

Categorical data will be presented using contingency tables with absolute and relative frequencies. Missing data will be considered as a category and included in the calculation of percentages, unless otherwise stated.

For time-to-event endpoints, Kaplan Meier (K-M) estimates will be provided and include number and percentage of events/censored, minimum, Q1, median, Q3 and maximum survival time and associated two-sided 95% CI obtained using the Brookmeyer-Crowley method. The progression-free survival rate and two-sided 95% CI at pre-specified time points will also be provided. In this case, Greenwood's formula will be used for the 95% CI.

For PK parameters and concentrations, summary statistics in the tabulation will include number of non-missing value, number below the lower limit of quantification (LLOQ), mean, standard deviation, minimum, Q1, median, Q3, two-sided 95% CI of the arithmetic mean, coefficient of variation (CV%), maximum, geometric mean, two-sided 90% CI of the geometric mean, geometric standard deviation [calculated as: geo standard deviation = exp ($SD_{log}$)], and geometric CV% [calculated as: geo CV% =SQRT(exp($SD_{log}^2$)-1)*100%]; where $SD_{log}$ is the standard deviation of the log-transformed values.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, Q1 and Q3 will be reported to one more decimal place than the raw data recorded in the database. The standard deviation will be reported to two more decimal places than the raw data recorded in the database. If raw data recorded have more than 1 decimal places, minimum and maximum will be reported to 1 decimal place, mean, median, Q1 and Q3 will be reported to 2 decimal place and standard deviation will be reported to 3 decimal place. Percentages will be reported with one decimal place. The CV% is reported as a percentage with 1 decimal places.

## 7.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher. For the PK analyses using non-compartmental method, WinNonlin version 8.1 or higher (Certara, L.P., Princeton, New Jersey) will be used.

# 8. STATISTICAL CONSIDERATIONS

## 8.1. MULTICENTER STUDIES

Center pooling will not be carried out for use in analyses for this study.
Statisctical tests and models will not be adjusted for the sites, and no analysis exploring the homogeneity of the results from one site to the other will be performed.

## 8.2. MISSING DATA

### 8.2.1. ADVERSE EVENTS

When the day of onset of an AE is missing:

- If month and year of onset of an AE is the same as the month and year of date of first administration of the study drug and the end date is not before the date of first dose, then the missing day is imputed by the day of date of first administration of the study drug
- Otherwise, the missing day is imputed by 1st of the month.

When the day and month of onset of an AE are missing

- If year of onset of an AE is the same as the year of date of first administration of the study drug and the end date is not before the date of first dose, then the missing day and month are imputed by the day and month of date of first administration of the study drug
- Otherwise, the missing day and month are imputed as January 1st

If onset date is completely missing:

- If AE end date is on/after the date of first administration of the study drug, then onset date is set to date of first administration of the study drug
- If AE end day or month are missing, then AE end day will be imputed as last day of the month and AE end month will be imputed as December.
    - If imputed end date is on or after the date of first administration of the study drug, then onset date is set to date of first administration of the study drug and AE is considered as treatment-emergent
    - If AE end date is prior to the date of first administration of the study drug, then onset date is not imputed, and AE is not considered as treatment-emergent

### 8.2.2. CONCOMITANT MEDICATIONS AND PROCEDURES/NON-PHARMACOLOGICAL TREATMENTS

- End date: Missing day will be imputed as the last day of the month, and missing month will be imputed as December.
- Start date: Missing day will be imputed as the 15th, and missing month will be imputed as June. If the start date is completely missing, then:
    - If the end date is prior to the date of first administration of the study drug, then the medication is considered as a pre-medictaion
    - If the end date is prior to the date of last administration of the study drug, then the medication is considered as a co-medication
    - If the end date is completely missing or after the date of last administration of the study drug, then the medication is considered as pre, co and post.

  If after imputation, start date > end date, then start date will be replaced by end date.

Subsequent anti-cancer therapies partial dates will be imputed as follow:

- End date: no imputation
- Start date: Missing day will be imputed as the 15th, and missing month will be imputed as June. If after imputation, start date <= date of last study treatment administration, then set start date to date of last study treatment administration + 1

  If after that, start date > end date, then start date will be replaced by end date.

### 8.2.3. EFFICACY

Missing efficacy data will be handled as described in section 17 of this analysis plan.

## 8.3. MULTIPLE COMPARISONS/ MULTIPLICITY

Given the exploratory nature of this study (i.e., no formal sample size computation was performed), no methods for handling multiplicity will be implemented for this study.

## 8.4. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

# 9. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

All endpoints such as demographics, baseline characteristics, safety, PK, PDy, etc. will be presented overall and by dose level for Part A and cohort for Part B.

All outputs will be presented for both Part A and Part B separately.

For Part B, the efficacy outputs will be reported by cohort.

# 10. DISPOSITION AND WITHDRAWALS

## 10.1. SUBJECT DISPOSITION

A summary on the SCR analysis set will include the number and the percentage of:

- Subjects screened (only frequency will be presented),
- Subjects screen failed with reasons
- Subjects enrolled ("Did the subject continue beyond screening" = yes as per the "Eligibility Criteria" eCRF page)
- Number of patients not treated with Debio 1143 and/or nivolumab, if applicable
- Treated subjects including
- End of treatment status (ongoing, discontinued) with reason for treatment discontinuation
- End of study status (completed, ongoing, discontinued) with reason for study discontinuation.
- Subjects in each of the study analysis sets

Subjects excluded from each analysis set out of the ITT/Safety analysis set will be tabulated by reason for exclusion.

All subject disposition data will be presented in data-listings. Screening failure and reasons will be listed separately. Reason of exclusion from each analysis set will be listed.

## 10.2. PROTOCOL DEVIATIONS

All deviations from the protocol will be reviewed and classified as major or minor prior to the database freeze for the final analysis of the Main study period. The full list of possible protocol deviations will be included in the study protocol deviation log which will include the classification (major or minor). The excel protocol deviation log will then be imported in SDTM.

Major protocol deviations will be summarized by deviation term in the ITT/Safety analysis set. A by-subject listing of all protocol deviations (major and minor) will be presented and will include the type of deviation and description.

# 11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for each analysis set (except the SCR analysis set) described in section 5 of this analysis plan.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years)
- Sex
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- Body mass index (BMI) ($kg/m^2$)
- Alcohol/Tobacco consumption
- ECOG-PS

A by-subject listing showing the demographic characteristics will be provided.

The baseline disease characteristics to be summarized will include:

- Stage at initial diagnosis
- Site of primary tumour
- Histological diagnosis
- Whether the current stage of disease is metastatic or not
- Locally advanced/unresectable disease

- Tumor Nodes Metastasis (TNM) classification at initial diagnosis (only for cohort 2)
- Time since initial diagnosis (months)
- Prior known PD-L1 expression status
- Molecular phenotype information (only for cohort 3 & 4)

All disease characteristics at baseline will also be listed.

## 11.1. DERIVATIONS

- BMI (kg/ $m^2$) = weight (kg)/ {[height (m)]$^2$}
- Time since initial diagnosis (months) = (treatment start date – initial diagnosis date)/30.4375

# 12. MEDICAL HISTORY

Medical history information will be presented for the SAF analysis set.

Medical history will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available at the time of the analysis.

Medical history are reported in "General Medical History" CRF page.

Medical history will be summarized by the number and proportion of subjects within each preferred term (PT), and system organ class (SOC).

Medical history will also be provided in a data-listing including the information on: SOC, PT, reported term, start and end date.

# 13. PRIOR ANTI-CANCER TREATMENTS

Prior anti-cancer treatments will be presented for the SAF analysis set.

Tabulations for prior anti-cancer treatments will include:

- Prior treatment with radiotherapy
  - Radiotherapy site or region
  - Reason for radiotherapy
- Prior treatment with systemic therapy
  - Intent of therapy

  - Therapy class/ Cancer therapy agent
  - Best overall response achieved over all and for each prior therapies
  - Reason for therapy discontinuation
- Prior anti-cancer surgery
  - Name of surgery
  - Location
  - Received surgery with curative intent? Best outcome achieved over all surgeries, presented separately for metastatic and locally advanced/unresectable patients as recorded on the cancer diagnosis eCRF

Additionally, prior anti-cancer therapies will be listed and will include:

- Prior radiotherapy: site or region, start/end date, total dose, dose per fraction, reason
- Prior systemic therapy: line of therapy, intent of therapy, cancer therapy agent (coded in WHODrug), therapy class, start/end date, reason for therapy discontinuation, date of progression (if applicable), best overall response
- Prior cancer surgery: name, location, date, whether the surgery was curative in intent, outcome

Additionally, prior and current anti-cancer treatments will be listed and will include:

- Prior systemic therapy: line of therapy, therapy class, cancer therapy agent (coded in WHODrug), start/end date, reason for therapy discontinuation, date of progression (if applicable), best overall response
- Study drug exposure (Debio 1143): primary tumor location, start/end date, time to progression or death, confirmed best overall response, ongoing on treatment
- Molecular phenotype: prior PDL-1 expression, applicable only to Cohort 3 and 4

# 14. MEDICATIONS

Medication information will be presented for the SAF analysis set.

Medications will be coded using the latest version of the WHODrug dictionary available at the time of the analysis.

See section 8.2.2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

Pre-medications are medications which started and stopped prior to the first dose of any study medication.

Concomitant medications are medications which:

- started prior to, on or after the first dose of any study medication but no later than the last administration of any study drug
- AND ended on or after the date of first dose of any study medication or were ongoing at the end of the study.

Post-medications are medications which started after the last dose of any study drug .

Pre- and concomitant medications will be summarized by anatomical therapeutic chemical (ATC) levels 2 and 4. All medications and procedures date will also be listed.

# 15. STUDY MEDICATION EXPOSURE

Exposure to any study medication, in weeks, will be presented for the RP2D (Part A only), SAF and EFF (Part B only) analysis sets.

The date of first study medication administration will be taken from the eCRF study drug exposure forms. The date of last study medication will be taken from the eCRF End of Treatment form.

The following information will be summarized in tables:

- Duration of exposure (weeks)
- Cumulative dose (mg), for cycle 1 and overall
- Number of administrations of Debio 1143, for cycle 1 and overall
- Number of infusions for Nivolumab (cycle 1 and full treatment period)
- Number of cycles for Nivolumab
- Details on treatment modifications
    - Number of patients having at least one Debio 1143 interruption, for cycle 1 and overall
    - Number of patients having at least one dose reduction (as defined in protocol section 5.4)
    - Summary of the number of interruptions of Debio 1143, for cycle 1 and overall
    - Summary of the number of patients having at least one interruption in the following durations (< 3 days, >= 3 days, >= 6 days, >= 14 days), for cycle 1 and overall
    - Summary of the cumulative duration of Debio 1143 interruption, for cycle 1 and overall
    - Incidence of action taken with Debio 1143/nivolumab and main reason for action taken

All exposure data as recorded exposure in the study drug exposure forms will be included in a listing. Also, data

recorded in the Debio 1143 and nivolumab accountability eCRFs will be listed.

## 15.1. DERIVATIONS

- Duration of exposure (weeks)
  - Debio 1143: (date of last dose of Debio 1143 – date of first dose of Debio 1143 +1)/7
  - Nivolumab: (date of last dose of nivolumab –date of first dose of nivolumab +1/7
- Actual Cumulative dose
  - Debio 1143 (mg): sum of the actual administered dose across all dosing dates
  - Nivolumab (mg): sum of the total dose administered across all cycles, if an infusion was interrupted then the total volume infused will be used to calculate the effective mg quantity administered (planned dose × (total volume infused/total volume prepared))
- For every unique interruption, defined as any occurrence of a 0 mg dose succeeding a non-0 mg dose, the duration of unique Debio 1143 interruption = (date of last day with Debio 1143 exposure form completed with actual dose of 0 mg – date of first day with Debio 1143 exposure form completed with actual dose of 0 mg) + 1

# 16. STUDY MEDICATION COMPLIANCE

Compliance to any study medication will be presented for the SAF analysis set.

The following compliance parameters will be summarized in tables:

- Treatment compliance (%) presented for both cycle 1 and full treatment period

## 16.1. DERIVATIONS

- Treatment compliance (%) = (actual cumulative dose /planned cumulative dose)*100

Planned dose by cycle:

- Debio 1143 (mg): 20 * 200= 4000
- Nivolumab (mg): 480

Planned cumulative dose:

- Debio 1143 (mg): Number of cycles started x Planned dose by cycle
- Nivolumab (mg): Number of cycles started x Planned dose by cycle

When Debio 1143 is ongoing, cycle starts if at least one dose of Debio 1143 > 0 is received on Day 1. Cycle period is defined from Day 1 of current cycle to day before Day 1 of the next cycle.

If Debio 1143 stopped but Nivolumab is ongoing, cycle period is defined as 28 days, continuing from the date of last Debio 1143 administration >0. (ie. For example, if last Debio 1143 administration is on 1APR21 corresponding to C4D17, next Nivolumab administration received on 14APR21 would corresponds to C5D2).

# 17. EFFICACY OUTCOMES

## 17.1. PRIMARY EFFICACY

For the purposes on the analyses described below, PD could be clinical progression (as recorded on the "End of Treatment" eCRF) or radiological progression (as recorded on the "overall response – RECIST v1.1" eCRF). In case of premature discontinuation with SD at the end of study (EOS) visit, this SD will be included in the derivation of the categorical efficacy parameters only if the assessment has been performed at least 35 days after treatment start.

### 17.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is confirmed ORR as per RECIST v1.1 and/or CGIG criteria (cohort 4, if applicable).

Confirmed objective response as per RECIST v1.1 is a confirmed best overall response (cBOR) of partial response (PR) or complete response (CR). The full derivation of confirmed BOR is be included in Section 17.2.1.2.

In the situation of lack of RECIST evaluation data (cohort 4 only), confirmed objective response as per GCIG criteria will be done using CA-125 levels. Patients will be scored as having attained a CA-125 response if they meet the GCIG-Rustin-modified criteria which require that there is at least a 50% reduction in CA-125 levels from a pre-treatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pre-treatment sample that is at least twice the upper limit of normal and within 2 weeks prior to starting treatment.

### 17.1.2. Missing Data Methods for Primary Efficacy Variable

No imputation methods will be used for the primary efficacy variable. If there is lack of available tumour assessment data due to treatment failure, then the patient will have a cBOR of not evaluable (NE).

### 17.1.3. Primary Analysis of Primary Efficacy Variable

Due to the exploratory nature of the trial, there will be no formal hypotheses testing. The primary efficacy analysis will be performed for the EFF analysis set.

At the final analysis for part B, a homogeneity Fisher exact test with a significance level of 0.3 will be conducted in the non-futile cohorts showing a confirmed response rate of at least 15% (>= 4 responders). If the primary endpoint homogeneity assumption is confirmed, the estimated confirmed ORR will be reported overall and by cohort based on the posterior beta distribution with a two-sided 95% credibility interval. Otherwise, if the homogeneity test does not reach significance level of 0.3, the estimated confirmed ORR and two-sided 95% credibility interval will be similarly reported in each cohort separately.

The efficacy of the futile cohorts and the cohorts with less than 15% confirmed response rate will be reported separately.

### 17.1.4. Sensitivity Analysis of Primary Efficacy Variable(s)

As sensitivity analyses, the primary efficacy analysis will be repeated on the ITT/Safety analysis sets.

## 17.2. Secondary Efficacy

The secondary efficacy analyses will be performed for the EFF and ITT/Safety analysis set.

### 17.2.1. Secondary Efficacy Variables & Derivations

#### 17.2.1.1. Unconfirmed objective response (uORR)

uORR is a unconfirmed best overall response (uBOR) of PR or CR. In the situation of lack of RECIST evaluation data (cohort 4 only), unconfirmed objective response as per GCIG criteria will be done using CA-125 levels. Patients will be scored as having attained a CA-125 unconfirmed response if they meet the GCIG-Rustin-modified criteria which require that there is at least a 50% reduction in CA-125 levels from a pre-treatment sample. This will be used during the futility monitoring analyses.

#### 17.2.1.2. Unconfirmed best overall response (uBOR)

The uBOR will be defined as the best response across all post-baseline tumour assessments that occur before the start of a new anti-neoplastic therapy. For example, a subject who has SD at the first assessment, PR at the second assessment, and PD at the last assessment has a BOR of PR. The order to obtain the BOR is the following: CR, PR, SD, PD, Not Evaluable (NE).

If a subject has no post-baseline tumour assessments, BOR will be NE.

#### 17.2.1.3. Confirmed best overall response (cBOR)

The cBOR will also be analysed. In this case, CR and PR need to be confirmed at a subsequent assessment, at least 4 weeks after the initial overall response assessment of CR/PR and before the start of a new anti-neoplastic therapy or administration of non-permitted concomitant medications. cBOR will be derived as described in the RECIST 1.1 guidance.

| Overall response first time point | Overall response subsequent time point* | cBOR |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[a] |
| CR | SD | SD, if minimum criteria for SD duration met, otherwise PD |
| CR | PD | SD, if minimum criteria for SD duration met, otherwise PD |
| CR | NE | SD, if minimum criteria for SD duration met, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD, if minimum criteria for SD duration met, otherwise PD |
| PR | NE | SD, if minimum criteria for SD duration met, otherwise NE |
| NE | NE | NE |

* Subsequent time point is not necessarily the direct subsequent scan (eg. PR-SD-PR will have PR as confirmed BOR)
[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would
depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans
suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

When SD is believed to be the best response, it must also be a minimum of 35 days after treatment day 1. If the

minimum time is not met, the subject's best overall response depends on the subsequent assessments. For example, a subject who has SD at the first assessment, PD at the second assessment and does not meet the minimum duration for SD, will have a best overall response of PD. The same subject lost to follow-up after the first SD assessment would be considered NE for BOR.

#### 17.2.1.4. Disease control

Disease control is derived as an uBOR of CR, PR or SD recorded at any point during the study.

#### 17.2.1.5. Progression-free survival (PFS)

PFS (months) is defined as (date of the first documented disease progression or death due to any cause, whichever occurs first – start date of treatment + 1)/30.4375.

The following censoring rules will be applied:

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No baseline and/or no post baseline assessment | Date of first dose | Censored |
| Disease progression documented between scheduled visits | Date of disease progression | PFS event |
| Death due to COVID-19 | Date of last adequate assessment | Censored |
| Death before first assessment | Date of death | PFS event |
| Death between adequate assessment visits | Date of death | PFS event |
| New systemic therapy started prior to disease progression | Date of last adequate assessment* prior to the start of subsequent antineoplastic therapy | Censored |
| Treatment discontinuation for undocumented disease progression after the last adequate assessment | Date of last adequate assessment | Censored |
| No documented disease progression or death | Date of last adequate assessment | Censored |

For patients in cohort 4, not evaluable by RECIST so being assessed by CA-125 criteria, the below table describes the criteria for defining progression and the date to be used in PFS derivation.

| GCIG-Rustin-modified definition of progressive disease according to CA-125 definition | | |
|---|---|---|
| | **Definition of progression** | **Date of progression** |
| Patients with elevated CA-125 before treatment and normalisation of CA-125 during treatment | CA-125 ≥ 2 X ULN documented on 2 occasions** | Date CA-125 is first elevated to ≥ 2 X ULN |
| Patients with elevated CA-125 pre-treatment that never normalises | CA-125 ≥ 2 X nadir value on 2 occasions** | Date CA-125 is first elevated to ≥ 2 X nadir value |

| | | |
|---|---|---|
| Patients with CA-125 in normal range pre-treatment | CA-125 ≥ 2 X ULN documented on 2 occasions** | Date CA-125 is first elevated to ≥ 2 X ULN |

**Repeat CA-125 anytime but normally not less than 1 week after the first elevated CA-125 level. CA-125 levels in samples obtained after administration of mouse antibodies or within 4 weeks after surgery or paracentesis should not be considered.

In patients for whom response to treatment is evaluated by both RECIST and CA-125 criteria, the RECIST evaluation will be used.

The median PFS and the PFS rate at each months will be derived from the Kaplan-Meier curves, as described in section 7.6.

#### 17.2.1.6. Duration of response (DoR)

DoR (months) is defined as (date of the first documented disease progression or death due to any cause, whichever occurs first – date of the initial response (PR or CR) or date of first reduction of 50% in CA-125 + 1)/30. 4375. It will be calculated only for subjects with a uBOR of CR/PR or at least a 50% reduction in CA-125 levels from a pre-treatment sample. Subjects that are lost-to-follow-up before disease progression will be censored at the date of their last adequate tumour assessment (i.e. a tumour assessment not showing NE) that occur before the start of a new anti-neoplastic therapy.

The median DoR and the DoR rate will be derived from the Kaplan-Meier curves, as described in section 7.6.

#### 17.2.1.7. Overall survival (OS)

OS (months) is defined as (date of death due to any cause – the start date of treatment +1)/30. 4375. Subjects with no documented death will be censored at the last date known to be alive (i.e. latest date collected in the eCRF).

The median OS and the OS rate at 12 months will be derived from the Kaplan-Meier curves, as described in section 7.6.

#### 17.2.1.8. CA-125 results

The CA-125 are collected on the tumor marker eCRF for cohort 4 only.

### 17.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLES

No imputation methods will be applied to the secondary efficacy variables. All details regarding how to handle lack of tumour assessment data and censoring is described in section 17.2.1

### 17.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

#### 17.2.3.1. Analysis of uORR

The uORR will be presented with absolute and relative frequencies in each cohort separately. No homogeneity test will be performed. This analysis will only be carried out for futility monitoring analyses.

#### 17.2.3.2. Analysis of uBOR, cBOR and disease control

uBOR, cBOR and DCR will be presented using contingency tables with absolute and relative frequencies. For part B, exact 95% confidence intervals will also be presented.

A spider plot will be produced showing the percentage change in sum of longest diameters (SOLD) over time. The profiles will continue until PD, death or lost-to-follow up, whichever occurs first. The spider plot will show key milestones such as time of initial response, first appearance of a new lesion and initial RECIST progression. Additionally, the thresholds for PD and PR will be displayed on the plot. For part A, the plot will be displayed by dose level and for part B, by cohort. For part B, a plot will also be produced for each cohort separately.

A waterfall plot will be produced showing the best percentage change in SOLD. The percentage change from baseline (for each patient) and patients having a BOR of CR or PR will be indicated in the plot. Additionally, the thresholds for PD and PR will be displayed on the plot. For part A, the plot will be displayed by dose level and site of primary tumour. For part B, the plot will be displayed by cohort only.

A vertical bar plot will be produced showing the patient's best overall response. For part A, the uBOR will be presented by dose level. For part B, a separate plot will be produced for both uBOR and cBOR and will be presented by cohort.

#### 17.2.3.3. Analysis of PFS, DoR and OS

For time-to-event endpoints, Kaplan Meier (K-M) estimates will be provided and include number and percentage of events/censored, minimum, Q1, median, Q3 and maximum survival time and associated two-sided 95% CI obtained using the Brookmeyer-Crowley method. The progression-free survival rate and two-sided 95% CI at pre-specified time points will also be provided. In this case, Greenwood's formula will be used for the 95% CI.

Additionally, a swimmers plot displaying key milestones will be produced. For each subject, the time from treatment start until end of follow-up will be represented (from treatment start to last date known to be alive or date of death). In addition, the following information will be displayed: SD/PR/CR duration and any period of re-treatment post-PD, time of end of treatment (if applicable) and the time of any dose reductions. For part A, the plot will be displayed by dose level and for part B, a seprate graph will be created for each cohort.

#### 17.2.3.4. Analysis of CA-125

Actual values and change from baseline of CA-125 will be summarised by visit.

### 17.2.4. SENSITIVITY ANALYSIS OF SECONDARY EFFIACY VARIABLES

A sensitivity analysis will be performed by censoring the OS at the time of start of a new systemic anti-cancer therapy.

Another sensitivity analysis will be performed by censoring the OS at the time of death due to COVID-19, if applicable

## 17.3. EXPLORATORY EFFICACY

### 17.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

#### 17.3.1.1. BOR by iRECIST

After a patient has had an initial overall response of PD using RECIST criteria the patient will be followed-up using iRECIST.

The iRECIST BOR will be defined as the best response using iRECIST criteria across all time points. The order to obtain the iRECIST BOR is the following: iRECIST Complete Response (iCR), iRECIST Partial Response (iPR), iRECIST Stable Disease (iSD), iRECIST Unconfirmed Progressive Disease (iUPD) and iRECIST Confirmed Progressive Disease (iCPD).

The table below gives examples of assignments of iRECIST BOR:

| | Timepoint response 1 | Timepoint response 2 | Timepoint response 3 | Timepoint response 4 | Timepoint response 5 | iBOR |
|---|---|---|---|---|---|---|
| Example 1 | iCR | iCR, iPR, iUPD, or NE | iCR, iPR, iUPD, or NE | iUPD | iCPD | iCR |
| Example 2 | iUPD | iPR, iSD, or NE | iCR | iCR, iUPD, or NE | iCR, iPR, iSD, iUPD, iCPD, or NE | iCR |
| Example 3 | iUPD | iPR | iPR, iSD, iUPD, or NE | iPR, iSD, iUPD, NE, or iCPD | iPR, iSD, iUPD, NE, or iCPD | iPR |
| Example 4 | iUPD | iSD or NE | iPR | iPR, iSD, iUPD, or NE | iPR, iSD, iUPD, iCPD, or NE | iPR |
| Example 5 | iUPD | iSD | iSD, iUPD, or NE | iSD, iUPD, iCPD, or NE | iSD, iUPD, iCPD, or NE | iSD |
| Example 6 | iUPD | iCPD | Any | Any | Any | iCPD |
| Example 7 | iUPD | iUPD (no iCPD) | iCPD | Any | Any | iCPD |
| Example 8 | iUPD | NE | NE | NE | NE | iUPD |

### 17.3.2. Analysis of Exploratory Efficacy Variables

The iRECIST BOR will be presented using contingency tables with absolute and relative frequencies.

Additionally, an alternative spider plot will be produced. This will be the same as described in section 17.2.3.2 except the profile will continue until iRECIST iCPD, death or lost-to-follow up, whichever occurs first. Each patients iRECIST BOR (or CA-125 response if no RECIST evaluation available) will displayed.

All efficacy data recorded in the following eCRFs will be listed: tumour marker, target lesions assessment, non-target lesions assessment, new lesions – RECIST, new lesions – iRECIST, overall response – RECIST and overall response iRECIST.

# 18. Safety Outcomes

All outputs for safety outcomes will be based on the SAF analysis set except the DLT summaries and listing which will be on the RP2D analysis set.

## 18.1. ADVERSE EVENTS

AEs as recorded in the Adverse Events eCRF will be coded using the most up-to-date version of the MedDRA central coding dictionary at the time of analysis.

TEAEs are defined as AEs that started or worsened in severity on or after the first dose of any study medication and prior to the last date of nivolumab + 5 months or the earliest date of new anticancer therapy – 1 day, whichever occurs first.

See section 8.2.1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

AEs will be graded according to NCI-CTCAE version 5.0

An overall summary of number of subjects within each of the categories described in the sub-sections below, will be provided as specified in the templates.

Listings will include TEAEs, Non-TEAEs and TEAEs leading to discontinuation of Debio 1143.

### 18.1.1. ALL TEAES

TEAEs will be presented by the following:

- System Organ Class/Preferred Term (SOC/PT, by cycle)
- SOC/PT & worst grade (by cycle)
- SOC/PT & worst grade (by cycle for cycle ≥ 2, updating denominator for each cycle with the number patients receiving at least one dose of nivolumab in that cycle)
- PT & pooled worst grade (pooling grade 1-2 and grade 3-4)

### 18.1.2. DLTS

DLTs are TEAEs where the question for DLTs in the eCRF is selected as “yes”. DLTs will need to be confirmed when making dose escalation decision.

An additional table will be presented showing the number of patients, by dose level, in each category with regards to number of DLTs (0, 1, >=2).

A vertical bar plot will be produced showing the number of evaluable patients and the number of patients having at least one DLT.

### 18.1.3. TEAEs WITH GRADE 3 OR HIGHER

TEAEs with grade 3 or higher are those events recorded on the eCRF where "NCI CTCAE Grade V5.0 Criteria" is answered as "Grade 3", "Grade 4" or "Grade 5".

TEAEs with grade 3 or higher will be presented by the following:

- SOC/PT and relatedness to study drugs (related to Debio 1143, related to nivolumab and related to both)
- PT and relatedness to study drugs
- SOC/PT and by cycle

### 18.1.4. TEAEs RELATED TO DEBIO 1143

TEAEs related to Debio 1143 are those events recorded on the eCRF where "Causal Relationship to Debio 1143" is answered as "Reasonable causal relationship".

TEAEs related to Debio 1143 will be presented by the following:

- SOC/PT
- SOC/PT & worst grade
- SOC/PT, worst grade and by cycle
- PT & worst grade

### 18.1.5. TEAEs RELATED TO NIVOLUMAB

TEAEs related to nivolumab are those events recorded on the eCRF where "Causal Relationship to Nivolumab" is answered as "Reasonable causal relationship".

TEAEs related to nivolumab will be presented by the following:

- SOC/PT
- SOC/PT & worst grade
- PT & worst grade

### 18.1.6. TEAEs RELATED TO BOTH DEBIO 1143 AND NIVOLUMAB

TEAES related to both Debio 1143 and Nivolumab are those events which meet both the criteria described in sections 18.1.4 and 18.1.5.

TEAEs related to both will be presented by the following:

- SOC/PT

- SOC/PT & worst grade
- PT & worst grade

### 18.1.7. TEAEs Leading to Dose Reduction of Debio 1143

TEAEs leading to dose reduction of Debio 1143 are those events recorded on the eCRF where "Action taken with Debio 1143" is answered as "Dose reduced".

TEAEs leading to dose reduction of Debio 1143 will be presented by the following:

- SOC/PT & by cycle
- PT

### 18.1.8. TEAEs Leading to Interruption of Debio 1143

TEAEs leading to interruption of Debio 1143 are those events recorded on the eCRF where "Action taken with Debio 1143" is answered as "Dose omitted" or "Treatment delayed".

TEAEs leading to interruption of Debio 1143 will be presented by the following:

- SOC/PT & by cycle
- PT

### 18.1.9. TEAEs Leading to Discontiuation of Debio 1143

TEAEs leading to dose discontinuation of Debio 1143 are those events recorded on the eCRF where "Action taken with Debio 1143" is answered as "Treatment permanently discontinued".

TEAEs leading to dose discontinuation of Debio 1143 will be presented by the following:

- SOC/PT & by cycle
- PT

### 18.1.10. TEAEs Leading to Nivolumab Infusion Rate Reduction

TEAEs leading to nivolumab infusion rate reduction are those events recorded on the eCRF where "Action taken with nivolumab" is answered as "Infusion rate reduced".

TEAEs leading to nivolumab infusion rate reduction will be presented by the following:

- SOC/PT & by cycle
- PT

### 18.1.11. TEAEs Leading to Nivolumab Interruption

TEAEs leading to nivolumab interruption are those events recorded on the eCRF where "Action taken with nivolumab" is answered as "Infusion interrupted".

TEAEs leading to nivolumab interruption will be presented by the following:

- SOC/PT & by cycle
- PT

### 18.1.12. TEAEs Leading to Discontiuation of Nivolumab

TEAEs leading to dose discontinuation of Nivolumab are those events recorded on the eCRF where "Action taken with Nivolumab" is answered as "Treatment permanently discontinued".

TEAEs leading to dose discontinuation of Nivolumab will be presented by the following:

- SOC/PT & by cycle
- PT

### 18.1.13. Serious Adverse Events (SAEs)

SAEs are AEs recorded on the eCRF where "Was event serious?" is answered as "Yes".

Treatment-emergent SAEs will be presented by the following:

- SOC/PT and relatedness to study drugs (related to Debio 1143, related to nivolumab and related to both)
- SOC/PT and by cycle

A separate listing of all SAEs will be presented.

### 18.1.14. TEAEs Leading to Death

TEAEs leading to death are those events recorded on the eCRF where the "Results in death" option is selected.

TEAEs leading to death will be presented by SOC/PT. A listing of all AEs leading to death will be presented.

### 18.1.15. Most common TEAEs

The analysis described in section 18.1.1 will be repeated but only presenting AEs where the overall percentage is ≥ 10%. Same analysis will be performed for AEs where the overall percentage is ≥ 5%. These will presented by the

following:

- SOC/PT and by cycle
- PT

### 18.1.16. Adverse Events Of Special Interest (AESIs)

AESIs (as described in protocol section 9.1.6) are AEs recorded on the eCRF where "Is this an adverse event of special interest" is answered as "yes".

Treatment-emergent AESIs will be presented by the following:

- SOC/PT & by cycle
- SOC/PT & worst grade

A vertical bar plot will be produced showing the number of patients experiencing an AESI presented by worst grade and by cycle.

## 18.2. Deaths

If any subjects die during the study as recorded on the "Death" page of the eCRF, the information will be presented in a summary table and a data listing.

## 18.3. Laboratory Evaluations

Results from the laboratory will be included in the reporting of this study for Haematology, Chemistry, Virology and Endocrinology. A list of laboratory assessments to be included in the outputs is included in the protocol (section 8.2.2.4 and as a footnote to table 8-6: schedule of assessments).

Presentations will use SI Units.

Quantitative laboratory measurements reported as "< LLOQ", i.e. below the lower limit of quantification (BLQ), or ">ULOQ", i.e. above the upper limit of quantification (ULQ), will be converted to the lower limit of quantification (LLOQ) or the upper limit of quantification (ULOQ) for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< LLOQ" or ">ULOQ" in the listings.

The following summaries will be provided for each lab parameter:

- Actual and change from baseline by visit (for quantitative measurements)
- Worst on-treatment CTCAE grade for each gradable parameter

- Shift using CTCAE grades from baseline to the worst on-treatment value
- Shift from baseline to the worst on-treatment value using the low / normal / high / (low and high) classification (only for non-gradable parameters)
- Incidence of maximum grade on treatment presented overall and by cycle, updating denominator for each cycle with the number patients receiving at least one dose of nivolumab in that cycle (only for gradable parameters)
- For patients having a grade 3/4 value:
    - Time to First Grade 3/4 Toxicity and Time to Resolution:
        - Time to recovery to grade <=2
        - Time to recovery to grade <=1
        - Time to full recovery (grade 0)
    - Conservative duration: (first assessment showing improvement (lower than grade 3/4) – date when analyte first graded 3/4 + 1)
    - Non-conservative duration: (last date analyte graded 3/4 (before grade ≤ 2) – date when analyte first graded 3/4 + 1)
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.
- Listing of notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities).
- Listing of Pregnancy Test (serum and/or urine).
- Scatter plots showing pre-treatment vs. lowest/highest on-treatment levels will be presented for each laboratory parameter.
- A vertical bar plot showing the worst grade experienced for each parameter

### 18.3.1. LABORATORY SPECIFIC DERIVATIONS

No specific laboratory derivation will be performed.

### 18.3.2. LABORATORY REFERENCE RANGES

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

### 18.3.3. CTC GRADING FOR LABORATORY DATA

Laboratory measurements will be graded using the NCI-CTCAE version 5.0 as defined in the following: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

For some gradable parameters, the CTCAE can be reassessed by the investigator. For any tables or figures which mention "CTCAE grade" in the sections above, the investigator grade should be used for these parameters.

The following analytes required investigator input:

- Amylase (Increase)
- Lipase (Increase)
- Potassium (increase & decrease)
- Sodium (increase & decrease)
- Hemoglobin (decrease)
- White cell count (Increase)
- Albumin (decrease)
- Calcium (increase & decrease)

These parameter will be flagged in related tables.

## 18.4. ECG EVALUATIONS

Results from the central ECG data will be included in the reporting of this study. The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcB Interval (msec)
- QTcF Interval (msec)
- Heart rate (HR) (beats per minute [bpm])
- RR interval (msec)
- Derived HR (msec), calculated as 60000/RR interval [for data checking only: should be within 5% of HR]
- Overall evaluation of ECG:
  - Normal
  - Abnormal (not Clinically Significant)

- Abnormal, Clinically Significant (ACS)

The mean of the triplicate values will be used for descriptive statistics.

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- Shift from baseline according to markedly abnormal criteria for absolute quantitative measurements
- Listing of all ECG assessment results flagging markedly abnormal criteria (displaying both individual measurements and mean of the triplicates)

### 18.4.1. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- Absolute values for QRS interval will be classified as:
  - < 50 msec
  - > 110 msec

- Absolute values for QT interval, QTcB interval and QTcF interval will be classified as:
  - > 450 msec
  - > 480 msec
  - > 500 msec

- Change from baseline for QTcB interval, and QTcF interval will be classified as:
  - >30 msec increase from baseline
  - >60 msec increase from baseline

For the markedly abormal criteria summary, each individual triplicate should be use.

## 18.5. Vital Signs

The following vital sign measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Temperature ($^0$C)

- Weight (kg)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Shift from baseline according to markedly abnormal criteria
- Listing of all vital signs assessment results flagging markedly abnormal criteria
- Box plots of actual values and change from baseline over time:
  - At least 3 cycles will be displayed
  - For part A, a separate plot will be produced for each dose level and then overall
  - For part B, one plot indicating the patients' cohort will be produced
- Scatter plots showing pre-treatment vs. lowest/highest on-treatment levels for each vital signs parameter.

### 18.5.1. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative vital signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

| Variable | Unit | Low | High |
|---|---|---|---|
| Weight | kg | Percentage change from baseline ≤ -20% | None |
| SBP | mmHg | ≤ 90 mmHg OR change from baseline ≤ -20 mmHg | ≥ 140 mmHg OR change from baseline ≥ 20 mmHg |
| DBP | mmHg | ≤ 60 mmHg OR change from baseline ≤ -20 mmHg | ≥ 90 mmHg OR change from baseline ≥ 20 mmHg |
| Heart rate | Bpm | ≤ 50 bpm OR change from baseline ≤ -20 bpm | ≥ 100 bpm OR change from baseline ≥ 20 bpm |

## 18.6. ECOG-PS

ECOG-PS will be presented as contingency tables by assessment timepoint. In addition, a shift table showing worst (higher score) on-treatment result will be presented. All ECOG-PS results will also be included in a listing.

# 19. PHARMACOKINETICS

Pharmacokinetics analysis will be performed on safety analysis set. Rather than excluding patients and create PK analysis set, some PK data may be excluded as not valid due to protocol violations/deviations or events with potential to significantly affect the concentration data (examples include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results, time windows or concomitant use of prohibited medications). Unscheduled sample and observation fulfilling any of the exclusion criteria will be excluded from summary statistics.

## 19.1. PHARMACOKINETIC CONCENTRATIONS

Individual PK blood sample collection times, derived sampling time deviations, and plasma concentrations of Debio 1143 and Debio 1143-MET1 and serum concentrations of nivolumab will be listed and figures will be presented for Cycle 1 Day 1. Time deviations will be calculated in reference to Debio 1143 administration or nivolumab infusion as specified in Table 8-1, Table 8-2, and Table 8-3 of protocol and taking into account the windows of tolerance specified in Table 8-5 of protocol.

Time deviations (actual sampling time outside the windows of tolerance specified in Table 8-5 of protocol) will be considered only relevant and a reason for data exclusion from PK analysis in case of pre-dose concentrations. All other post-dose time deviations will be considered not relevant and therefore concentrations will always be included in the PK analysis.

Should ADA samples be analyzed for serum ADA entities, results for nivolumab ADA will be listed, and ADA concentrations will be summarized only for ADA positive samples.

For each analyte, concentrations will be summarized using descriptive statistics (described in Section 7.6) by cycle, study day and scheduled time. In addition, the summaries for nivolumab concentrations will be stratified by Nivolumab regimen (240 mg or 480 mg) as applicable and summaries for Debio concentrations will be stratified by Debio regimen (150 mg or 200 mg).

Concentrations that are missing will be omitted from the calculation of descriptive statistics.

To derive PK parameters and for summary statistics (except for calculations involving logarithmic transformations), concentrations reported as BLQ will be considered as 0 when they occur before the first quantifiable concentration. BLQ concentrations occurring after the first quantifiable concentration will be set to 1/2 LOQ.

For summary statistics where calculation involves logarithmic transformations (including geometric mean calculation), plasma levels BLQ will be set to 1/2 LOQ.

Considering limited data and sample collections in patients, samples collected outside of protocol specified time windows will still be included in the summaries; except, pre-dose Debio 1143 (and Debio 1143-MET1) and nivolumab samples collected after administration of the respective drug will be excluded from the summaries.

For each analyte, figures of geometric mean concentrations ± geometric standard deviations on log10/linear scales will be presented. By-patient plots of individual concentration-time profiles log10/linear scales will also be presented.

## 19.2. PHARMACOKINETIC PARAMETERS

The PK parameters for Debio 1143, Debio 1143-MET1, and nivolumab in Part A and Part B will be calculated by noncompartmental method described below. If deemed appropriate, a population PK approach may be used and will be reported separately.

The actual elapsed time from Debio 1143 dose administration will be used for Debio 1143 and Debio 1143-MET1 analyses, and the actual elapsed time from the start of Nivolumab infusion will be used for Nivolumab analysis.

The PK calculated using available data include:

| **Debio 1143 and Debio 1143-MET1:** | | **Part A** | **Part B** |
|---|---|---|---|
| $C_{max}$ (ng/mL) | Maximum concentration in plasma obtained directly from the observed concentration versus time data. | Cycle 1 day 1, day 8, day 15 and day 22<br>Cycle 3 day 1 and day 15<br>Cycle 6 day 1 | Cycle 1 day 1, day 8, day 15 and day 22<br>Cycle 3 day 1 and day 15<br>Cycle 6 day 1 |
| $C_{max}$ (µmol/L) | $C_{max}$ (ng/mL) transformed in molar units according to analyte molecular weight* | Cycle 1 day 1, day 8, day 15 and day 22<br>Cycle 3 day 1 and day 15<br>Cycle 6 day 1 | Cycle 1 day 1, day 8, day 15 and day 22<br>Cycle 3 day 1 and day 15<br>Cycle 6 day 1 |
| $t_{max}$ (h) | Time of maximum concentration, obtained directly from the observed concentration versus time data. | Cycle 1 day 1, day 8, day 15 and day 22<br>Cycle 3 day 1 and day 15<br>Cycle 6 day 1 | Cycle 1 day 1, day 8, day 15 and day 22<br>Cycle 3 day 1 and day 15<br>Cycle 6 day 1 |
| $AUC_{(0\text{-}4h)}$ (ng·h/mL) | Area under the concentration-time curve in plasma from zero (pre-dose) to the 4-hour post-dose time point. | Cycle 1 day 1, day 8, day 15 and day 22<br>Cycle 3 day 1 and day 15 | Cycle 1 day 1 and day 22<br>Cycle 3 day 1 |

| Debio 1143 and Debio 1143-MET1: | | Part A | Part B |
|---|---|---|---|
| $AUC_{(0-4h)}$ (h·µmol/L) | $AUC_{(0-4h)}$ (ng·h/mL) transformed in molar units according to analyte molecular weight* | Cycle 1 day 1, day 8, day 15 and day 22<br>Cycle 3 day 1 and day 15 | Cycle 1 day 1 and day 22<br>Cycle 3 day 1 |
| $AUC_{(0-8h)}$ (ng·h/mL) | Area under the concentration-time curve in plasma from zero (pre-dose) to the 8-hour post-dose time point. | Cycle 1 day 1, day 8 and day 15<br>Cycle 3 day 1 and day 15 | |
| $AUC_{(0-8h)}$ (h·µmol/L) | $AUC_{(0-8h)}$ (ng·h/mL) transformed in molar units according to analyte molecular weight* | Cycle 1 day 1, day 8 and day 15<br>Cycle 3 day 1 and day 15 | |
| $C_{trough}$ (ng/mL) | Minimal concentration in plasma before next dose obtained directly from the observed concentrations versus time | Cycle 1 day 3, day 8, day 17 and day 22<br>Cycle 3 day 3 and day 17 | Cycle 1 day 8 and day 22 |
| $C_{trough}$ (µmol/L) | $C_{trough}$ (ng/mL) transformed in molar units according to analyte molecular weight* | Cycle 1 day 3, day 8, day 17 and day 22<br>Cycle 3 day 3 and day 17 | Cycle 1 day 8 and day 22 |
| $MR\_AUC_{(0-4h)}$ | $AUC_{(0-4h)}$ Metabolic ratio: Ratio of Debio 1143-MET1 $AUC_{(0-4h)}$/Debio 1143 $AUC_{(0-4h)}$, calculated as ratio for molar units | Cycle 1 day 1, day 8, day 15 and day 22<br>Cycle 3 day 1 and day 15 | Cycle 1 day 1 and day 22<br>Cycle 3 day 1 |
| $MR\_AUC_{(0-8h)}$ | $AUC_{(0-8h)}$ Metabolic ratio: Ratio of Debio 1143-MET1 $AUC_{(0-8h)}$/Debio 1143 $AUC_{(0-8h)}$, calculated as ratio for molar units | Cycle 1 day 1, day 8 and day 15<br>Cycle 3 day 1 and day 15 | |

| Debio 1143 and Debio 1143-MET1: | | Part A | Part B |
|---|---|---|---|
| MR_$C_{max}$ | $C_{max}$ Metabolic ratio: Ratio of Debio 1143-MET1 $C_{max}$/Debio 1143 $C_{max}$, calculated as ratio for molar units | Cycle 1 day 1, day 8, day 15 and day 22<br>Cycle 3 day 1 and day 15<br>Cycle 6 day 1 | Cycle 1 day 1, day 8, day 15 and day 22<br>Cycle 3 day 1 and day 15<br>Cycle 6 day 1 |

| Nivolumab: | | Part A | Part B |
|---|---|---|---|
| $C_{trough}$ (ng/mL) | Minimal concentration in serum before next dose obtained directly from the observed concentrations versus time | Cycle 1 day 15<br>Cycle 3 day 1 and day 15 (only those with 240 mg dose)<br>Cycle 6 day 1 | Cycle 1 day 15<br>Cycle 3 day 1 and day 15 (only those with 240 mg dose)<br>Cycle 6 day 1 |
| $AUC_{tau}$ (ng·h/mL) | Area under the concentration-time curve in plasma from zero (pre-dose) to end of the dosing interval of 15 days | Cycle 1 day 1 (from day 1 pre-dose to pre-dose day 15)<br>Cycle 3 day 1 (from day 1 pre-dose to day 15 (only those with 240 mg dose) | Cycle 1 day 1 (from day 1 pre-dose to pre-dose day 15) |
| $AUC_{inf}$ (ng·h/mL) | Area under the concentration-time curve in plasma from time of dosing extrapolated to infinity | Cycle 1 day 1 and day 15 | |
| Css (ng/mL) | Concentration at steady-state, concentration observed at the end of nivolumab infusion | Cycle 1 day 1 and day 15<br>Cycle 3 day 1 and day 15 (only those with 240 mg dose) | Cycle 1 day 1 and day 15<br>Cycle 3 day 1 and day 15 (only those with 240 mg dose) |
| CL (L/h) | Clearance calculated as Rate of nivolumab infusion/Css | Cycle 1 day 1 and day 15<br>Cycle 3 day 1 and day 15 (only those with 240 mg dose) | Cycle 1 day 1 and day 15<br>Cycle 3 day 1 and day 15 (only those with 240 mg dose) |

*Debio 1143 molecular weight: 561.71 g/mol; Debio 1143-MET1 molecular weight: 476.61 g/mol

The following PK parameters for Nivolumab will be listed only as supporting information for $AUC_{inf}$, but will not be summarized:

$\lambda_z$ Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination.

| | |
|---|---|
| $t_{1/2}$, Interval | The time interval (h) of the log-linear regression to determine $\lambda_z$ |
| $t_{1/2}$, N | Number of data points included in the log-linear regression analysis to determine $\lambda_z$. |
| Rsq | Goodness of fit statistic for calculation of $\lambda_z$ (Regression coefficient). |
| $\%AUC_{ex}$ | Percentage of $AUC_{(0\text{-inf})}$ obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC_{(0\text{-inf})}\times 100]$. |

The AUCs for Debio 1143, Debio 1143-MET1, and Nivolumab will be calculated using linear up/log down trapezoidal summation.

For Nivolumab $AUC_{inf}$, if either or both of the following criteria are not met, the corresponding $AUC_{inf}$ value will be listed only but excluded from the summary:

- Rsq (in the calculation of $\lambda_z$) > 0.85
- $\%AUC_{ex}$ < 15.0%

For each analyte, individual PK parameters will be listed and summarized using descriptive statistics (described in Section 7.6) by cycle and study day. In Part A, the summaries will be presented for each dose level and overall. In Part B, the summaries will be presented for each cohort and overall. In addition, the summaries for nivolumab concentrations will be stratified by Nivolumab regimen (240 mg or 480 mg) as applicable.

## 19.3. EXPLOROTORY PHARMACOKINETIC ANALYSES

The correlations between Debio 1143 PK parameters and efficacy/safety parameters will be produced in an exploratory manner. Analyses of correlation between various Debio 1143 PK parameters with clinical response, QTcF and selected lab parameter grades are described below.

Debio 1143 PK parameters vs. Clinical response

Boxplots will be produced where the y-axis displays the value of $C_{max}$ at Cycle 1 Day 1. The x-axis will display each level of confirmed objective response as described in section 17.1.1. Similarly, the box plots will be produced for each level of cBOR as described in section 17.2.1.3. Finally, a scatter plot with a fitted regression line will be produced, with the x-axis presenting the value of $C_{max}$ at Cycle 1 Day1 and the y-axis presenting the best change in tumor size (lowest percentage change from baseline in SOLD).

The analysis described above will be repeated for the following parameters: $C_{max}$ at Cycle 1 Day 8 and $C_{trough}$ at Cycle 1 Day 8.

Debio 1143 PK parameters vs. QTcF

A scatter plot with a fitted regression line will be the produced, with the y-axis presenting the absolute QTcF value at Cycle 1 Day 1/0.5 – 2 hours post-dose and the x-axis presenting the value of $C_{max}$ at Cycle 1 Day1. Horizontal dashed lines will be added for each of the markedly abnormal criteria for QTcF as described in section 18.4.1. Similarly, the same regression plot will be produced except for the relative change from baseline in QTcF.

The analysis described above will be repeated for the following:

- $C_{max}$ at Cycle 1 Day 1 vs. QTcF at cycle 1 day 1/4 – 6 hours post-dose
- $C_{max}$ at Cycle 1 Day 1 vs. change from baseline in QTcF at cycle 1 day 1/4 – 6 hours post-dose
- $C_{max}$ at Cycle 1 Day 8 vs. QTcF at cycle 1 day 8/0.5 – 2 hours post-dose
- $C_{max}$ at Cycle 1 Day 8 vs. change from baseline in QTcF at cycle 1 day 8/0.5 – 2 hours post-dose
- $C_{max}$ at Cycle 1 Day 8 vs. QTcF at cycle 1 day 8/4 – 6 hours post-dose
- $C_{max}$ at Cycle 1 Day 8 vs. change from baseline in QTcF at cycle 1 day 8/4 – 6 hours post-dose
- $MR_{Cmax}$ at Cycle 1 Day 1 vs. QTcF at cycle 1 day 1/0.5 – 2 hours post-dose
- $MR_{Cmax}$ at Cycle 1 Day 1 vs. change from baseline in QTcF at cycle 1 day 1/0.5 - 2 hours post-dose
- $MR_{Cmax}$ at Cycle 1 Day 1 vs. QTcF at cycle 1 day 1/4 – 6 hours post-dose
- $MR_{Cmax}$ at Cycle 1 Day 1 vs. change from baseline in QTcF at cycle 1 day 1/4 – 6 hours post-dose
- $MR_{Cmax}$ at Cycle 1 Day 8 vs. QTcF at cycle 1 day 8/0.5 – 2 hours post-dose
- $MR_{Cmax}$ at Cycle 1 Day 8 vs. change from baseline in QTcF at cycle 1 day 8/0.5 – 2 hours post-dose
- $MR_{Cmax}$ at Cycle 1 Day 8 vs. QTcF at cycle 1 day 8/4 – 6 hours post-dose
- $MR_{Cmax}$ at Cycle 1 Day 8 vs. change from baseline in QTcF at cycle 1 day 8/4 – 6 hours post-dose

Debio 1143 PK parameters vs. Lab Parameter Grades

Boxplots will be produced where the y-axis displays the value of Cmax at Cycle 1 Day 1. The x-axis will display the maximum grade in AST experienced during Cycles 2 and 3 combined. This will be repeated for the following parameters ALT, bilirubin, amylase and lipase and for the value of Cmax at Cycle 1 Day 8.

# 20. PHARMACODYNAMICS

Pharmacodynamics at baseline, at any scheduled visit, and the corresponding fold changes (log2) from baseline will be presented using descriptive statistics. The maximum increase on-treatment will be similarly presented, along with its fold change from baseline. On-treatment period defined as the time from the date of first dose to the date of last dose.

Graphics displaying PDy parameters absolute values and fold changes from baseline will be presented as individual curves and mean curves (±standard deviation) vs. time.

# 21. REFERENCES

Cunanan K. M., Iasonos A., Shen R., Begg C. B., Gönen M. (2017) An efficient basket trial design. Statististics in Medicine, 36(10):1568-1579. doi: 10.1002/sim.7227

# APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

## Style

TFLs and TFL shells will be produced using font size 9, Courier New. Size 8 may exceptionally be used when space requires it (particularly for Listings), but no smaller fonts are permitted.

No italic or bold font will be used: the font will remain consistent throughout the whole output.

All tables will be produced in landscape orientation, with margins that meet the ICH E3 criteria: '*Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (E.U. and Japan) and 8.5 x 11" paper (U.S.). The left-hand margin should be sufficiently large that information is not obscured by the method of binding.'*

No vertical delineation will be used in Tables or Listings.

Horizontal delineation across the entire printable part of the page will be used between the title and the column headers, between the column headers and the table body and between the table body and the footnotes.

One blank line will be left between the last table title and the first horizontal delineator.

The last horizontal delineator will appear immediately before the first footnote, i.e. with no separating blank line.

One blank line will be left after each block of statistics, e.g. the set of descriptive statistics for a single variable, or a single timepoint, or the frequency table for a single variable.

Variable names and categories, statistic names etc, appearing in the leftmost columns will be left-justified. Statistics in the treatment columns will be centred.

## Study Outline Template

The Study Outline Template forms part of the template for the deliverable: this is the part that will appear identically on each page of each output (with the exception of the page number which will change but should appear in the same position on all pages).

The Study Outline Template is composed of template headers and template footers, as follows:

- Template Header line 1: Debio xxxx-xxx {the study number}, left justified, and 'Debiopharm International S.A.', left justified
- Template Header line 2: Deliverable (e.g. 'Interim Analysis', 'Final Analysis'), left justified and 'page x of n' right justified (representing the page number within the output, not within the whole set of outputs)

- Template Footer: Only one footnote will appear on the template for the deliverable: the Database extraction date (combined with the cut-off date for a partial database lock where applicable): this footnote will be right-justified, on the last line. The date(s) will use the format DDMMMYYYY.

Additional TFL-specific titles and footnotes are described below.

The number of pages in an output is unlimited.

## TFL Titles

Each TFL will have at least three title as follows:

1. Output Type (Table/Figure/Listing) + Output number (14.x.x.x.x)
2. Main title, i.e. Description of TFL
3. Population

These titles will start on the first line available after the study outline template (i.e. the third line of the output) and will be centre-justified.

Where necessary an optional 4th TFL title may be used to denote a subgroup, strata, dose group, treatment group, treatment cycle, sensitivity analysis etc. This 4th title will appear on the line below the third title and will be left-justified

The full title is repeated on all pages of an output.

All TFL titles will use capitalisation of the first letter of all words, except insignificant words such as ‘to’, ‘at, ‘and’, etc., which will appear in lowercase. Acronyms will appear completely in uppercase.

Within a deliverable (such as ‘Interim Analysis’ or ‘Final Analysis’) the first title (Table x.x.x.x, Listing x.x.x.x or Figure x.x.x.x) must be unique. In other words, the numbering is unique within the type of output within the output. Titles 2, 3 and 4 need not be unique within a deliverable. The numbering may be repeated for subsequent deliverable: in this case the name of the deliverable acts as the unique output identifier.

## TFL Footnotes

The TFL footnotes clarifying the content of the table will be presented in the following order:

1. Output-specific footnotes related to the whole output: these will be left-justified, using sentence case and containing no annotation or numbering.

2. Output-specific footnotes relating to a specific point in the output: these will be left-justified, using

sentence case, and will reference the specific location in the output relating to the footnote using sequential numbering [1], [2]

3. Program path and name: these will be left-justified, and will use leading dots to replace the basic server path where all studies are programmed as long as the location can be uniquely identified from the detail provided, e.g. …..\Debio xxxx\xxx\Final\Pgm\ProgramName.sas
4. Creation date and time: these will be left-justified and will use the format 'Created DDMMMYYYY at HH:MM'. The actual date and time of creation will be used, and not the SAS system time, which only indicates when the SAS session was initiated.
5. (if applicable): Source {Source: Listing x.x.x.x}: this will be right-justified and can appear on the same line as the left-justified creation date.

TFL footnotes will use sentence case, i.e. capitalisation only of the first letter, and any proper nouns.

The full set of TFL footnotes is repeated on all pages of an output.

### TFL Numbering

The numbering specified in the TFL shells should follow the ICH E3 guideline for Clinical Study Reports.

The numbering specified in TFL shells should be sequential and as expected to be used in the CSR. It should be kept up to date if changes are made to the TFL shells

There is no limit to the number of levels of numbering, so insertions can be easily managed.

A number can be used for e.g. a figure as well as a table but must be unique within an output type, i.e. no two tables or two figures will use the same number.

No letters or words should be used in the numbering system.

TLFs produced for a particular deliverable should only be a subset of CSR outputs. Therefore, outputs produced for more than one deliverable may use the same numbering: the difference is reflected in the Study Outline Template.

## Table Columns

Columns on tables and listings should be spread across the available with of the printable page.

Columns of a table consist of the **label column** and the **treatment columns.**

After taking account of the space required for the label column, the treatment columns will be equally spaced over

the available remaining page-width.

Treatment groups should be presented in the following order:

- Varying doses of the same Investigational product in increasing order, then a Total column.
- Placebo-controlled study: Investigational product first, placebo second. A Total column is added for baseline data only. The Total column should not be presented for post-baseline data unless specified in the SAP.
- Active comparator study: Investigational product first, then active comparator, and if relevant, placebo arm last. A Total column is added for baseline data only. The Total column should not be presented for post-baseline data unless specified in the SAP.
- Various doses within multiple regimens: increasing dose within the regimen, then an overall regimen column, and repeat by regimen. Split each regimen on a separate page where necessary.

Treatment descriptions in the column headers should be specified for the whole study and remain the same in each output. They will be repeated on each page of an output.

The header of the label column will be left-aligned.

The headers of the treatment columns will be centre-aligned.

The headers of the treatment columns will include the description of the treatment arm and the number in that group in the relevant population, in the format (N=xxx), appearing on its own line.

Additional details may be included in a third line, such as in Adverse Event / Concomitant Medication tables where they require ‘n (%)’ or ‘n (%) events’ to specify the statistics that are included in the columns, where it is not possible or feasible to specify these in a variable label.

## Statistical Comparisons

For studies containing statistical comparisons, inferential statistics and p-values can be placed either in an additional column after all treatment groups, or in additional rows, depending on the study design. In either case, the TFL shells and the final output must make it clear which columns are being compared.

All p-values will be presented to three decimal places.

P-values less than 0.001 should be presented as ‘<0.001’, and p-values greater than 0.999 should be presented as ‘>0.999’.

# Document Approval Signature(s)

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