Statistical Analysis Plan (SAP)

Version 3.0: 12DEC2018

A phase I/IIa trial to evaluate the safety and efficacy of the combination of the oncolytic immunotherapy Pexa-Vec with the PD-1 receptor blocking antibody nivolumab in the first-line treatment of advanced hepatocellular carcinoma (HCC)

PROTOCOL N° TG6006.01

EUDRACT N° 2016-000085-32
IND N° 17439
NCT03071094

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CONFIDENTIAL

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Study phase: I/IIa

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COORDINATING INVESTIGATOR: [redacted]

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DOCUMENT APPROVAL

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LIST OF ABBREVIATIONS

AE	Adverse Event
AFP	Alpha-Foetoprotein
BCLC	Barcelona Clinic Liver Cancer
BMI	Body Mass Index
bpm	Beats per minute
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose Limiting toxicity
DoR	Duration of Response
eCRF	Electronic Case Report Form
EOT	End of Treatment
EOS	End of Study
ETOH	Ethanol
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HR	Hazard Ratio
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
INT	Integer part
IT	Intratumoral
ITT	Intent To Treat
IU	International Unit
ISC	Independent Safety Committee
IV	Intravenous
LLN	Lower Limit of Normal
MH	Medical History
MIN	Minimum

MAX	Maximum
N	Number
NA	Not Applicable
NASH	Non-Alcoholic Steato Hepatitis
NCI	National Cancer Institute
NCS	Not Clinically Significant
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAF	Safety
SC	Subcutaneous
sd	Standard deviation
SD	Stable Disease
SI units	International System of units
SOC	System Organ Class
TTP	Time To Progression
ULN	Upper Limit of Normal

1 UPSTREAM DOCUMENTATION

The following documents were used to prepare the Statistical Analysis Plan:

- Study protocol TG6006.01 Version dated 22 December 2017
- eCRF Version 6.0 dated 16 February 2018

2 STUDY DESIGN

This is an open-label single-arm Phase I/IIa study.

2.1 Phase I

The Phase I part is a single cohort enrolling 6 patients at standard Pexa-Vec and nivolumab doses, i.e. $1x10^9$ pfu and 240 mg, respectively.

Pexa-Vec will be administered by intra-tumoral infusion on D1, D15 and D29, and nivolumab by intravenous infusion on D15 and D29 and then every two weeks. The study will document dose-limiting toxicities (DLTs) and landmark AEs. A landmark AE is an anticipated effect of the combination defined as an increase in severity of hepatic cytolysis (doubling of AST – ALT baseline blood concentrations), or significant deterioration of hepatic function (INR, bilirubin), or increase in incidence or severity of immune-related AEs, or increase in number or severity of Pexa-Vec-related skin lesions.

The first patient will be monitored for the safety scheduled up to D29, i.e. the end of the DLT monitoring period, before 5 additional patients can be enrolled. In addition, a security time interval of 2 weeks between enrolments of consecutive patients will apply. This time interval is appropriate to prevent additional patients to be exposed to potential acute or subacute toxic events observed in the previous patients.

If more than one DLT is observed in the first 6 patients, or in case of the occurrence of a landmark AE, one de-escalation dose regimen will apply on a cohort of 6 additional patients. Depending on the DLT profile relative to the known toxicity of each component of the combination and upon the recommendation of the Independent Safety Committee (ISC), the doses of Pexa-Vec and nivolumab will be either $3x10^8$ pfu for Pexa-Vec and 240 mg q2 weeks for nivolumab OR 10^9 pfu for Pexa-Vec and 240 mg q3 weeks for nivolumab

In case no more than one DLT and no occurrence of any landmark AE is observed in 6 patients at the initial Phase I dose level or, if relevant, at the de-escalation dose level, the Phase IIa part of the study could start.

2.2 Phase IIa

The Phase IIa part consists of a single patient cohort. The initiation of the Phase IIa part and the dose level to apply will be determined based on the DLTs and landmark AEs observed in Phase I part and following a review by the ISC of all safety data collected in Phase I. No security time intervals will apply between two consecutive patients.

2.3 Number of patients and evaluable patients

The Phase I part of the study will be conducted in a few sites to enroll between 6 and 12 evaluable patients, should no or one dose de-escalation level be applied, respectively.

Evaluable patients for Phase I are patients having completed the DLT period (ending on Day 29) and received all 3 Pexa-Vec intra-tumoral treatments and 2 nivolumab infusions, or having exhibited a DLT.

In the Phase IIa part of the study, the number of participating countries and sites will be expanded to about 3 countries and 10 sites, in order to enroll a total of 30 evaluable patients, including Phase I patients evaluable for Phase II, and comparable in terms of population and treatment regimen (same inclusion/exclusion criteria and same treatment regimen).

Evaluable patients for Phase IIa are patients having received at least 2 administrations of Pexa-Vec and 2 administrations of nivolumab and undertaken at least one post-baseline radiological assessment and/or with any evidence of disease progression other than CT scan.

The maximal number of patients to be enrolled in the Phase I/IIa study may is then 42 evaluable patients. Considering a 10% rate of non-evaluable patients who will have to be replaced for the implementation of principal per protocol analysis, the final maximal patient enrolment in the study would be 47 patients.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary objectives and endpoints

The primary objective of the study is:

- In Phase I: To evaluate the safety profile of intratumoral (IT) Pexa-Vec combined with intravenous (IV) nivolumab in patients with advanced HCC. Corresponding endpoints will consist of (S)AEs graded according to NCI-CTCAE version 4.03, DLTs and landmark AEs
- In Phase IIa: To evaluate the anti-tumor activity and efficacy of IT Pexa-Vec combined with IV nivolumab in patients with advanced HCC. The primary endpoint will be the Overall Response Rate (ORR) according to RECIST 1.1

3.2 Secondary objectives and endpoints

3.2.1 Secondary objectives

In Phase I, the secondary objective is to assess signals of efficacy.

In Phase IIa, the secondary objectives are to assess safety and signals of efficacy in terms of additional radiological endpoints (all imaging endpoints evaluated by RECIST 1.1), survival and viral load.

3.2.2 Secondary endpoints

- Both in Phase I and Phase IIa

  Disease Control Rate (DCR) at 4 months

  Disease Control Rate (DCR)

  Time to Progression (TTP)

  Duration of Response (DoR)

  Progression Free Survival (PFS)

  Overall Survival (OS)

  Blood viral load (HCV, HBV when appropriate)

- Additionally, in Phase I

  ORR

- Additionally, in Phase IIa

  (S)AEs after grading per NCI-CTCAE version 4.03

3.3 Exploratory objectives

[redacted]

4 STUDY DURATION

This study started in July 2017 (First Patient In). Recruitment is expected to be completed by Feb 2019 and the study is expected to be completed by Feb 2020 (Last Patient Last Visit).

5 TREATMENT PLAN

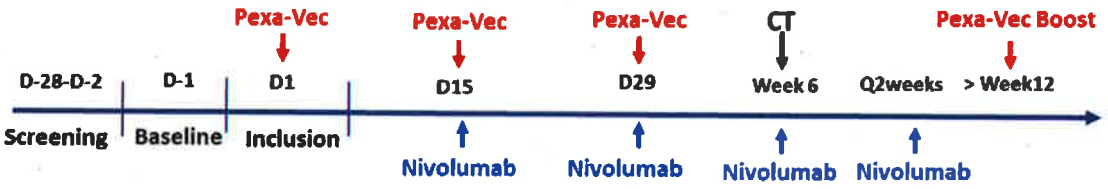
5.1 Randomization

No randomization is planned in this study.

5.2 Duration of Treatment

Patients of Phase I and Phase IIa will receive intratumoral (IT) injections of Pexa-Vec in combination with nivolumab intravenous (IV) infusions:

- Pexa-Vec injections will be performed on D1, D15 and D29. Additional Pexa-Vec boosts may be performed from Week 12 after discussion on a case by case basis between the investigator and Transgene, on the grounds of individual patient benefit.
- Nivolumab will be given from D15 every 2 weeks as long as a clinical benefit is observed with no unacceptable toxicity.



6 DEFINITION OF THE POPULATIONS TO BE ANALYZED

For Phase I part and safety evaluation, the Safety (SAF) population will be the primary population and the DLT population will be used for decision for de-escalation or continuation for Phase IIa part. DLT population will also be used for secondary endpoints of efficacy.

For Phase II part, the primary dataset will be the Per Protocol population and efficacy analyses will be repeated for Intent-To-Treat population. Safety population will be used for safety evaluation as secondary endpoint.

6.1 Subject populations

Safety population

All patients enrolled into the study who received at least one dose of either IMP will be included in the safety analysis. The patients will be analyzed according to the treatment actually received (Pexa-Vec or Pexa-Vec + Nivolumab) and this population will be the primary dataset for safety evaluation.

DLT population

In Phase I, patients who received all 3 Pexa-Vec and 2 nivolumab administrations and completed the DLT period and/or patients having exhibited a DLT after at least one dose of either IMP will be included in DLT population. The patients will be analyzed according to the treatment actually received and this dataset will be used for safety evaluation.

Per protocol (PP) population

In Phase IIa, patients without major protocol deviations who received at least 2 administrations of Pexa-Vec and 2 administrations of nivolumab and undertaken at least one post-baseline assessment and/or with any evidence of disease progression other than CT scan will be included in PP population. Comparable patients from Phase I (same inclusion/exclusion criteria and same treatment regimen) without major protocol deviation who received at least 2 administrations of Pexa-Vec and 2 administrations of nivolumab and undertaken at least one post-baseline assessment and/or with any evidence of disease progression other than CT scan will also be included in PP population. The patients will be analyzed according to the treatment planned and this dataset will be the primary dataset for efficacy evaluation.

Intent-to-treat (ITT) population

All patients enrolled into the study who received at least one dose of either IMP will be included in the intent to treat. The patients will be analyzed according to the treatment planned and this population will be used for efficacy evaluation.

6.2 Major protocol deviations

A list of deviations identified by programming and by listing review will be defined by CRO biostatistician according to the Protocol and in agreement with Transgene before the database export. Programs shall be created by the CRO biostatistics team to identify deviations. Furthermore, deviations reported by Data Management and CRAs shall also be taken into account to define the final deviations list of the Study.

Anticipated but not limited major deviations are:

- Failure to complete all 3 IT Pexa-Vec injections and 2 nivolumab IV infusions in the absence of DLT in the Phase I part, 2 IT Pexa-Vec injections and 2 nivolumab IV infusions in the Phase IIa part,
- No histological confirmation of HCC,
- Previous systemic therapy for HCC,
- Child-Pugh score beyond A, or deteriorated hepatic function beyond score, or advanced cirrhosis diagnosis based on albuminemia, INR, bilirubin blood levels and clinical symptoms: uncontrolled ascites or esophageal varices, etc.
- ECOG PS > 1,
- Prohibited concomitant medications or no withdrawal of anti-hypertensive, anticoagulant or anti-platelet medications within protocol-specified conditions,
- Immunodeficiency,
- Pregnancy and breast-feeding.

GCP deviations (including protocol deviations, applicable SOPs deviations etc) must be tracked. Transgene shall be provided with a deviation listing before the data review meeting. The criticality of each deviation will be established in agreement with Transgene during the data review meeting (at the latest) in order to define the different populations for analyses.

7 STATISTICAL DESIGN

7.1 Sample size determination for Phase IIa part

Hypotheses

As the patient survival benefit may be correlated with either radiological response of tumors or/and prolonged stabilization of the disease, the analysis of efficacy will consider ORR as primary endpoint. Sample size justification will use available data on ORR, as such: in a Phase I/II trial, 8/42 (19%) patients with previously treated HCC experienced an objective response when treated with single-agent nivolumab (El-Khoueiry et al., ASCO 2015). Therefore, a response rate of 15%-20% with the combination of Pexa-Vec + nivolumab in not previously treated HCC patients would be considered disappointing, while a response rate of 35% or more would be promising and would encourage further study of the regimen in these patients. The null hypothesis for response rate H0 is set at 15%, the alternate hypothesis of efficacy is set at H1=35%, the type I error α is set at 5% one sided and the power is set at 80%.

Statistical Design

Under these hypotheses, a two-stage group sequential design using alpha and beta spending function approach with Lan DeMets spending function (O'Brien-Fleming efficacy boundaries and non-binding Pocock futility boundaries) will be used leading to a maximum sample size of 30 evaluable patients and an interim analysis based on 15 evaluable patients (implemented in EAST® 6.3) with a test proportion with normal approximation to the binomial distribution.

7.2 ISC for Phase I

ISC will review safety data when 6 evaluable patients for Phase I have reached their Day 29 visit:

- In case no more than 1 Dose-Limiting Toxicity (DLT) is observed in 6 patients and no occurrence of any landmark AE (see section 2.1), then accrual in the Phase IIa part of the study will start at the same dose level.
- In case of more than one DLT is observed, or the occurrence of a landmark AE, one de-escalation regimen is planned to Level -1, depending on the DLT profile relative to the known toxicity of each component of the combination, as judged by the ISC:
    - 3 bi-weekly IT injections of $3x10^8$ pfu for Pexa-Vec and 240 mg q2 weeks for nivolumab OR
    - 3 bi-weekly IT injections of 10^9 pfu for Pexa-Vec and 240 mg q3 weeks for nivolumab.

7.3 Interim analysis for Phase II

7.3.1 Purpose of Interim Analyses

When 50% of evaluable targeted number of patients have reached their W12 visit or discontinued the study treatment due to disease progression, an interim analysis will be conducted to either stop the trial for futility (and not expose more patients to the combination), or stop the trial for efficacy or continue the trial as planned.

7.3.2 Planned Schedule of Interim Analyses

At interim analysis, enough patients will be treated to obtain a total of 15 evaluable patients, including comparable patients of the Phase I part (same inclusion/exclusion criteria and same treatment regimen) still evaluable for Phase II part.

7.3.3 Stopping Rules

If there are 3 or fewer responses in these 15 patients (20% of responders or less), the study could be stopped for futility. If there are 6 or more responses in these 15 patients (40% of responders or more), the null hypothesis will be rejected and the combination will be considered to have a substantial activity to be of further interest and the study could be stopped for efficacy. Otherwise 15 additional evaluable patients will be accrued for a total of 30.

7.4 Final Statistical Analysis

At final analysis, enough patients will be treated to obtain a total of 30 evaluable patients, including comparable patients of the Phase I part (population, treatment regimen) still evaluable for Phase II part.

The null hypothesis will be rejected if 8 or more responses are observed in the 30 evaluable patients (26.7% of responders or more) with a power of 80% and a type I error of 5%. It should nevertheless be reminded that given the mechanism of action of the drugs involved and the effects of immunotherapy on tumor behavior, ORR may not be the best measure of anti-tumor activity. For this reason, consideration will be given to DCR, TTP and survival parameters prior to deciding that the combination does not warrant further exploration.

Drafts TFLs will be produced and reviewed before the database export to ensure that no critical data is missing and to check potential inconsistency in the database.

Follow-up statistical analyses will be conducted when the study will be closed and after the database lock.

7.5 Data Review Meeting

A data review meeting will occur:

- Before analysis for Independent Safety Committee at the end of Phase I
- Before Interim Analysis
- Before final statistical analysis

The purpose of data review meeting will be to discuss the following issues:

- Resolve the last issues in data
- Completeness of data capture and coding
- Presence of non-resolved adverse events

- Action to be taken to any of this above data issues
- Classification of protocol deviations into minor and major deviations
- Allocation of subjects to various analysis populations
- Finalize the statistical analysis plan

Data listings will be produced by CRO before the data review meeting, the list of listings to produce will be defined in agreement with Transgene.

7.6 Missing data

Measurements that were not performed or not recorded are treated as missing data.

No imputation will be done for missing data, excepted for calculation of duration with missing and incomplete dates for birth and adverse events (AE). Missing data will be noted as missing in appropriate tables/listings.

Imputation Rules for Partial Birthdates:

- If the month and year are present, impute the day by the 15th day of that month.
- If only the year is present, impute by July 1st of that year.

Imputation Rules for Partial or Missing Start Dates for AE:

- If the month and year are present, impute the day by the first day of that month. If the month and year are the same as those of the date of first dose of IMP, impute the day with the day of first treatment administration.
- If only the year is present, impute by January 1st. If the year is the same as the year of the date of first dose of IMP, impute by the date of first treatment administration.
- If the start date is entirely missing, impute by the date of first treatment administration.

Imputation Rules for Partial or Missing Stop Dates for AE:

- If the month and year are present, impute the day by the last day of that month.
- If only the year is present, impute by December 31st of that year.
- If the stop date is entirely missing, assume the event is ongoing.

7.7 Definitions and Derived variables

7.7.1 Definitions

Baseline: Unless otherwise specified, baseline is the last measurement taken prior to the first injection of IMP.

Study day:

For post-study treatment administration measurements, study day will be calculated using the start date of treatment as the origin, i.e. the study day will be calculated as (date of assessment) – (start date of study treatment) +1. Then study day 1 will be the first day of first study treatment administration.

For pre-study treatment administration measurements, the study day will be negative and calculated as (date of assessment) – (start date of study treatment).

Cut-off date: For a given analysis (interim, final and follow-up analysis), data in the database with a date prior to the cut-off date must be clean. The cut-off date will be the latest date considered for cleaning activities for a given lock.

Only data with an assessment date or event start date (e.g., vital sign assessment date or start date of an AE) prior to or on the cut-off date will be included in the statistical analysis. (Example: If cut-off date is 15JUN2016 then an AE starting on 15JUN2016 or before will be reported, whereas an AE with start date on 16JUN2016 will not be reported).

All AE or concomitant medications with start date before or on the cut-off date and end date after the cut-off date will be reported as 'continuing at the cut-off date'. The end data will be considered as missing data and will be displayed as such in listing.

7.7.2 Derived variables

The following conventions will be used:

- 1 month corresponds to 365.25/12=30.4375 days.
- 1 year corresponds to 365.25 days.

The following variables will be calculated:

- Age expressed in years: the age at informed consent form (ICF) signature presented in whole years (rounded down to the whole year)
  INT([date of ICF signature – date of birth +1]/365.25)
- Body Mass Index (BMI) expressed in kg/m^2: Weight (kg) / Height^2 (m^2)
- Duration of an event expressed in days: End date – Start date + 1

The following survival variables will be calculated:

- TTP expressed in months = (Date of first documented radiographic tumor progression – date of first treatment administration +1)/30.4375
  Or (Date of last evaluable tumor assessment – date of first treatment administration +1)/ 30.4375 in case of censoring.
- PFS expressed in months = (MIN(Date of first documented radiographic tumor progression, Date of death from any cause) – date of first treatment administration +1)/30.4375
  Or, (Date of last evaluable tumor assessment – date of first treatment administration +1)/30.4375 in case of censoring.
- OS expressed in months = (Date of death from any cause – date of first treatment administration + 1)/30.4375
  Or, (Date of last contact – date of first treatment administration +1) /30.4375 in case of censoring.
- DoR expressed in months for patients whose best overall response was CR or PR = (MIN(Date of first documented disease progression, date of death from underlying disease) – Date of first documented response +1)/30.4375
  Or, (Date of the last evaluable tumor assessment – Date of first documented response +1)/30.4375 in case of censoring.

The following variables will be derived for Pexa-Vec and Nivolumab treatment information:

- Duration of IMP exposure: expressed in weeks and calculated as

  [(Date of last IMP administration) - (Date of first IMP administration) +1]/7

- Relative Dose Intensity (%): expressed as a percentage and defined as the ratio of "delivered" to the "planned" dose intensity. The dose intensity is the total amount of IMP given a fixed unit of time. A Relative Dose Intensity of 100% indicates that the IMP was administered at the dose planned per protocol, without delay and without cancellations. It is calculated as

  100 x IMP Actual Dose Intensity / IMP Planned Dose Intensity

Study IMP parameters definitions for dose level 1 are defined in the following table to derive relative dose intensity.

	Pexa-Vec	Nivolumab
Dose schedule per protocol	10^9 pfu at D1, D15 and D29	240 mg every 2 weeks
Actual Dose	Actual dose expressed in pfu is defined as	Actual dose expressed in mg is defined as Total dose (mg); as

	(Total volume injected / Total volume prepared) x Dose Pexa-Vec (pfu); as reported in eCRF page "*Pexa-Vec IT injection*"	reported in eCRF page "*Nivolumab Administration*"
Actual Cumulative Dose	Actual Cumulative Dose expressed in pfu is defined as the sum of the actual doses	Actual Cumulative Dose expressed in mg is defined as the sum of the actual doses
Actual Dose Intensity (intensity per week)	Actual Dose Intensity expressed in pfu/wk is defined as Actual Cumulative Dose / [(Last administration - first administration + 14)/7]	Actual Dose Intensity expressed in mg/wk is defined as Actual Cumulative Dose / [(Last administration - first administration + 14)/7]
Planned Dose Intensity	5×10^8 pfu/week	120 mg/week

All laboratory parameters will be expressed in the International System (SI) of units and the intensity grade using CTCAE version 4.03. A grade of 0 will be assigned when the value is within normal limits. In the case a local laboratory normal range overlaps into the higher (i.e., non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of 0. When normal limits are missing and needed for intensity grade determination, the grade will be set at missing. If normal limits are missing but not needed, grade intensity will be calculated as usual with CTCAE ranges.

Laboratory values recorded as "value < x" or "value > x" will be handled as equal to:

- x – 0.001 if value recorded as "value < x"
- x + 0.001 if value recorded as "value > x"

for the calculation of descriptive parameters and for the value derived in SI units. Other methods could be investigated for specific parameters. In individual listings they will be presented as "< x" or "> x".

Calculated creatine clearance with Cockroft formula and Corrected Calcium will be also provided in table and listing.

Creatinine Clearance (CRCL) - Cockroft formula:

CRCL(Male) (mL/min) = 1.23 x weight (kg) x (140 - Age)/creatinine(umol/l)

CRCL(Female) (mL/min) = 1.04 x weight (kg) x (140 - Age)/creatinine(umol/l)

Corrected Calcium - Cockroft formula:

Corrected Calcium (mmol/L) = Serum Calcium (mmol/L) + 0.02 * (40 - albumin [g/L])

8 STATISTICAL METHODS

8.1 General principles

Statistical summaries will be produced using SAS® software version 9.4. The tables, listings and graphics will be prepared in landscape format.

Continuous variables will be described using: number of observations (N), arithmetic mean (Mean), standard deviation (sd), minimum (MIN), median (Median), the interquartile range (Q1-Q3) and maximum (MAX). One additional decimal point for mean, median, Q1 and Q3, and 2 additional decimal points for sd will be used. Data with more than 3 decimal places (if any), may not follow this rule: so 3 decimal places will be used.

Categorical variables will be presented using the number of observations (N) and percentages (%). Proportions will be displayed with one decimal and estimated with their exact (Clopper-Pearson) 95% CIs when appropriate.

All statistical testing will be two-sided at the 0.05 level without adjustments for multiplicity testing, unless specified otherwise. P-values will be presented to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001, even if it would normally round up to 0.001.

8.2 Patient enrollment and disposition

8.2.1 Screening status

The number of patients screened (who gave informed consent) will be displayed for each part of the study (Phase I/Phase IIa) by cohort (Cohort #1, Cohort #-1 and overall). All patients who failed to meet eligibility criteria after ICF signature will be considered as screening failure and reported in the study report. The number of these patients and the primary reason for non-inclusion will be also displayed. Percentages will be calculated over the number of patients screened.

A listing will be performed to present all screen failures with the reason(s) of non-inclusion.

8.2.2 Population

A disposition table will display, for Phase I part and by cohort (Cohort #1, Cohort #-1 and overall), the number and percentage of patients (percentages based on enrolled patients) with:

- Patients enrolled
- Patients included in the SAF population
- Patients included in DLT population

A listing will be displayed with the reason from exclusion from DLT population.

A disposition table will display for Phase IIa part and by cohort (Cohort #1, Cohort #-1 and overall) the number and percentage of patients (percentages based on enrolled patients) with:

- Patients enrolled
- Patients included in ITT population
- Patients included in the PP population
- Patients from Phase I included in Phase II PP population (no percentage)
- Total number of patients included in PP population (Phase I and Phase IIa, no percentage)

The number and percentage of patients who were not included in the PP population will be presented by cohort (Cohort #1, Cohort #-1 and overall) for Phase IIa with the main reason for non-inclusion. The main reason for non-inclusion in the PP will be listed.

The number and percentage of enrolled patients (ITT population) will be also presented by country and site.

8.2.3 Status at the end of study

The status of patients at the end of study (completed / not completed) will be presented for each part of the study (Phase I/Phase IIa) by cohort (Cohort #1, Cohort #-1 and overall). For a patient, the study is considered as 'Completed' if the reason for study treatment withdrawal ("*End of treatment*" form of eCRF) is ticked "*Progressive Disease*" or "*Maximum treatment duration (12 months)*". This analysis will be conducted in the safety population.

The number and percentage of patients having withdrawn the study will be summarized for each part of the study (Phase I/Phase IIa) by cohort (Cohort #1, Cohort #-1 and overall) with the primary reason of withdrawal. The percent will be based on the safety population.

8.3 Analysis of demographic and baseline characteristics

These analyses will be based on the SAF and DLT populations for Phase I and on PP and ITT populations for Phase IIa.

8.3.1 Demographic and baseline characteristics

The following demographic characteristics at baseline will be listed and summarized by cohorts (Cohort #1, Cohort #-1 and overall) with the following items:

- Country
- Gender
- Race (American Indian or Alaska Native / Asian / Black or African American …)
- Ethnicity (Hispanic or Latino / Not Hispanic nor Latino / Not collected)
- Age at consent (in years)
- Weight (in kg), Height (in cm) and BMI (in kg/m^2)
- Method of analysis for diagnosis (Histological / Cytological / Other)
- Differentiation of the tumor (Poorly / Moderately / Well differentiated / Not Evaluated)
- Etiology of HCC (HCV / HBV / NASH / ETOH / Other)
- Stage of HCC per BCLC (Stage 0 / Stage A / Stage B / Stage C / Stage D)
- Cirrhosis (Yes/No)
- ECOG performance status (0 / 1 / 2 / 3 / 4)
- Previous Cancer History (Yes/No)

Prior cancer therapy details will be listed and summarized by cohorts (Cohort #1, Cohort #-1 and overall) with the following items:

- Number of patients with previous cancer therapy
- Type of Therapy (Radiotherapy / Surgical resection / Radiofrequency ablation (RFA) / Chemoembolization (TACE) …)
- Setting (Adjuvant / Neo-Adjuvant / Therapeutic / Palliative / Other)
- Number of procedures / treatments
- Best Overall Response (CR / PR / SD / PD / NE)
- Surgical Resection (Complete / Partial)

The following baseline characteristics will be listed and summarized by cohorts (Cohort #1, Cohort #-1 and overall):

- Child-Pugh scoring: Encephalopathy, Ascites, Bilirubin, Albumin, Prothrombin Time or International Normalized Ratio and Total score
- Vital signs: systolic / diastolic blood pressure (in mmHg), heart rate (in bpm), respiratory rate (in bpm) and temperature (in °C)
- Physical examination results presented by Body System and status (normal / abnormal)
- Medical and surgical history including concomitant diseases (other than the studied disease) presented by SOC sorted by alphabetic order and PT within SOCs sorted by decreasing count according to the overall column.
- Signs and symptoms with CT-CAE grade presented by SOC sorted by alphabetic order and PT within SOCs sorted by decreasing count according to the overall column. "*Signs and Symptoms*" form of eCRF will be completed during Day 1 visit.
- Electrocardiogram: Overall results (Normal / Abnormal NCS / Abnormal CS)
- Thyroid function: TSH, FT3 and FT4.
- HIV/HBV/HCV (Positive / Negative / Not Done)

8.3.2 Concomitant diseases

Concomitant diseases are diseases present at the baseline visit and not listed in the exclusion criteria (eg, hypertension, diabetes).

Concomitant diseases will be included in the Medical History.

8.4 Stratification factors

No stratified analysis is planned in this study.

8.5 Protocol deviation summaries

All protocol deviations for enrolled patients will be presented by patient in data listings with a distinction between deviations at inclusion and deviations during the study.

The number of patients with at least one major protocol deviation will be summarized by type and overall with a distinction between deviations at inclusion and deviations during the study. All protocol deviations will be reviewed before database lock during the Data Review Meeting.

8.6 Treatments

The treatment information will be based on the SAF and DLT populations for Phase I and on both PP and SAF populations for Phase IIa.

8.6.1 Study treatment

The following information will be listed for each patient who received at least one administration of IMP and will be summarized by Cohort (Cohort #1, Cohort #-1 and overall):

- Total number of Pexa-Vec administrations (Table only)
- Number of administrations of Pexa-Vec
- Number of tumors treated with Pexa-Vec
- Cumulative dose of Pexa-Vec for all tumors (pfu)
- Pexa-Vec relative Dose Intensity (percentage)
- Duration of Pexa-Vec exposure (weeks)
- Total number of Nivolumab infusions (Table only)
- Number of infusion of Nivolumab
- Cumulative dose of Nivolumab (mg)
- Nivolumab relative Dose Intensity (percentage)
- Duration of Nivolumab exposure (weeks)

Another table will summarize the number of cancelled or not done administrations (no administration of IMP) and interrupted administration (IMP not fully administered) for each IMP (Pexa-Vec or Nivolumab) with the main reason of non-treatment or interruption for each IMP.

8.6.2 Prior and Concomitant medications

Prior and Concomitant medications are:

- Medications and/or non-drug therapies taken by the patient during the month before Day 1 of study treatment (i.e., start of the study treatment), continuing or not after the start of the study treatment
- All medications and non-drug therapies taken during the treatment period of the study starting from Day 1 up to 28 days after the last study treatment administration

The prior and concomitant medications will be coded using the WHO Drug Dictionary and will be presented by ATC code and Drug Name. A table with the frequency and percentage of patients with prior and concomitant medications will be displayed by cohort (Cohort #1, Cohort #-1 and overall).

8.6.3 End of treatment (EOT) and End of study (EOS) visits

The following information will be listed for each patient and will be summarized by Cohort (Cohort #1, Cohort #-1 and overall):

- Week of end of treatment visit defined as integer part of [Study Day / 7]
- Reason for study treatment withdrawal (Progressive Disease / Clinical progression / Occurrence of an unacceptable AE / Pregnancy / …)
- Week of end of study visit defined as integer part of [Study Day / 7]

8.7 Analysis of efficacy

All the efficacy analyses will be based on the PP population which is the primary dataset and will be analyzed and presented by Cohort (Cohort #1, Cohort #-1 and overall). Efficacy analyses will be repeated for ITT population for Phase IIa and for DLT population for Phase I.

All efficacy variables will be listed in dedicated listings by subject and the following summaries will be presented by Cohort (Cohort #1, Cohort #-1 and overall) in case of de-escalation in any part of the study:

- Continuous efficacy endpoints will be summarized using N, Mean, sd, Median, interquartile range (Q1-Q3), MIN, and MAX. If appropriate, log-normal variable will be log-transformed for descriptive statistics.
- Categorical efficacy endpoints will be summarized using number and percentage (with exact 95% CI).

- Survival efficacy endpoints will be presented using the number of events, number and percentage of censored patients, quartiles (Q1, median and Q3) and the associated 95% CI. A graphical representation will be done for these endpoints using a Kaplan-Meier curve with 95% CI.

8.7.1 Primary efficacy endpoint and analysis

For Phase IIa part the primary endpoint is the Overall response rate (ORR) which is the proportion of patients, whose best overall response is either CR or PR, confirmed at least 4 weeks after initial documentation. A test proportion with normal approximation to the binomial distribution will be used and null hypothesis will be rejected if 8 or more responses are observed in the 30 evaluable patients (26.7% of responders or more)

8.7.2 Secondary efficacy endpoints and analyses

The following secondary efficacy endpoints will be considered:

- Disease control rate (DCR) is the proportion of patients whose best overall response is either CR, PR, or SD.
- 4-month (18-week) DCR is proportion of patients whose best overall response is either CR, PR, or SD 4 months after D1 (using tumor assessments before Day 127).
- The Time to Progression (TTP) is the time from Day 1 to the date of first documented radiographic tumor progression. TTP does not include deaths. If a patient has not had a TTP event at the cut-off date for analysis, TTP will be censored at the date of last evaluable tumor assessment before the cut-off.
- Progression Free Survival (PFS) is the time from Day 1 to the date of first documented tumor progression or death due to any cause, whichever occurs first. If a patient has not had a PFS event and is not known to have died at the cut-off date for analysis, PFS will be censored at the date of last evaluable tumor assessment before the cut-off.
- Overall Survival (OS) is the time from Day 1 to the date of death due to any cause. If a patient is not known to have died at the cut-off date for analysis, survival will be censored at the date of last contact.
- Duration of overall Response (DoR) applies only to patients whose best overall response is CR or PR. The start date is the date of first documented response (CR or PR) and the end date is the date of first documented disease progression or the date of death due to underlying cancer. DoR will be censored if progression or death due to underlying cancer is not observed at the cut-off date for the analysis, or death to another cause than underlying cancer or start of further anti-cancer therapy. The censoring date will be the date of the last

evaluable tumor assessment.

- Tumor size (in mm) is defined as the sum of the diameters recorded for all target lesions as identified at baseline. Relative change from baseline in tumor size over time will be summarized and graphically represented. This value is automatically calculated in "Follow-up target lesions" form of eCRF.
- HBV DNA and HCV DNA viral load (and change from baseline) will be summarized for each visit.

For OS, the percent survivors over time will also be presented considering the proportions of patients alive at 6, 9, 12, 18, and 24 months, along with corresponding 95% CIs. At these timepoints the restricted mean survival time with 95% CI will be calculated.

For PFS, the percent of non-progressors over time will also be presented considering the proportions of patients having not progressed at 6, 9, 12, 18, and 24 months, along with corresponding 95% CIs. At these timepoints the restricted mean non-progression time with 95% CI will be calculated.

For Tumor size, a graphical representation will be done using a waterfall plot. This plot will display the best percentage change from baseline for each patient, sorted in descending order (using bar) and colored by the Best Overall Response (CR/PR/SD/PD).

8.7.3 Exploratory efficacy endpoints and analyses

Some exploratory analyses could be done using the following statistical methods:

- A Linear regression to study potential effects of covariates on continuous endpoints
- A logistic regression to study potential effects of covariates on categorical endpoints (such as ORR and DCR)
- A Log-rank test and/or a Cox model to study potential effects of covariates on survival endpoints (PFS, TTP, OS and DoR). Estimates of the HRs with 95% CIs will be obtained from a Cox regression model.

8.8 Analysis of safety

All the safety analyses will be performed on the SAF population which is the primary dataset for safety evaluation in Phase I and Phase IIa parts. Safety analyses will be repeated on DLT population in Phase I part.

8.8.1 Adverse Events

8.8.1.1 Definitions

From the date of signature of ICF and up to first IMP administration (i.e. before the patient receives any IMP) only SARs caused by a protocol-required procedure (e.g., related to invasive procedures such as blood sampling) will be collected and reported. AEs, SAEs, or procedure related ARs that occur during this period, and that are considered by the investigator as relevant to the patient condition, will be collected as a current medical history.

After the initiation of either IMP and up to 28 days after the last dose of IMP, all AEs and SAEs will be collected and recorded on the eCRF. SAEs will also be reported to Transgene.

SAEs occurring more than 28 days after the last dose of IMP, and evaluated by the Investigator as related to the IMP will be collected and reported to Transgene indefinitely even after end of study. Only SAEs occurring prior to end of study will be reported in the eCRF.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary using latest version available. NCI-CTCAE version 4.03, dated June 14, 2010 will be used.

All AEs will be reported on the "*Adverse Event*" section of eCRF.

Dose-limiting toxicity (DLT) is defined as any of the following treatment-related adverse events (AEs) and occurring during the first 4 weeks (up to D29), in the Phase I part of the study; grades are referring to NCI CTCAE v. 4.03:

1. All Grade 3-4 non-hematologic toxicity that represent a 2-grade increase over baseline, excluding:
   - Untreated or inadequately treated nausea, vomiting and diarrhea,
   - Untreated or inadequately treated fever > 40.0°C lasting less than 24 hours (Grade 3); only fever > 40.0°C lasting more than 24 hours (Grade 4) qualifies for DLT
   - Alopecia,
   - Grade 3 fatigue that returns to grade 2 or less within 7 days,
   - Grade 3 laboratory/metabolic abnormalities, other than ALT or AST, that are not considered clinically significant and that return to grade 2 or less within 72 hours.
2. Any Grade ≥ 3 treatment-related acute immune-related AE involving major organs, such as: immune-related pneumonitis, colitis, nephritis, hepatitis, endocrinopathies, immune-related rash and other rare but severe immune-related reactions.

3. Grade ≥ 3 injection site reaction.

4. AST or ALT ≥ 10xULN, even if asymptomatic, unless it is related to a definite progression of liver metastases or another clearly identifiable etiology; doubling of AST or ALT that is concurrent with a doubling of the total bilirubin.

5. Any toxicity at least possibly related to study therapy that results in a delay in treatment of 2 or more weeks.

6. Hematological:

- Grade ≥ 3 or ≥ 2-grade increase over baseline of neutropenia lasting for more than 7 days.
- Neutropenic fever.
- Grade 4 thrombocytopenia or grade 3 thrombocytopenia with clinically significant bleeding.

7. Cardiac: association of the 3 following cardiac abnormalities

- Left ventricular ejection fraction (LVEF) less than the lower limit of normal (LLN), as assessed by echocardiography and symptomatic due to drop in ejection fraction, responsive to intervention,
- Increase of blood troponin T or I above the upper limit of normal (ULN),
- Any ECG abnormality consistent with a Grade 3 cardiac disorder.

8.8.1.2 AEs Analysis

Adverse Event (AE)

For the analyses, the number and percentage of patients will be summarized in a frequency table by body system organ class (SOC) and preferred terms (PT) as per MedDRA dictionary. The number of events will be also summarized in the same table. The table will be displayed by SOC sorted alphabetically and by PT within SOC sorted by decreasing count according to the overall column. Each patient will be counted only once within each classification (SOC / PT).

AEs subject to Immediate Reporting

AEs subject to immediate reporting are the AEs with the item "*Event subject to immediate reporting*" ticked "*Yes*" in "*Adverse Event*" form of the eCRF.

Serious Adverse Events (SAEs)

The SAEs are the adverse events with the item "*Is this adverse event considered as Serious?*" ticked "*Yes*" in "*Adverse Event*" form of the eCRF. If the item is missing, the AE will be considered

as Serious.

AEs related to Study procedure

AEs related to Study Procedure are the AEs with the item "*Is this event related to study procedure*?" ticked "*Yes*" in "*Adverse Event*" form of the eCRF. If the data is missing, the AE will be considered as related to Study Procedure.

AEs related to Pexa-Vec

AEs related to Pexa-Vec are the AEs with the item "*Is this event related to Pexa-Vec*?" ticked "*Yes*" in "*Adverse Event*" form of the eCRF. If the data is missing, the AE will be considered as related to Pexa-Vec.

AEs related to Nivolumab

AEs related to Nivolumab are the AEs with the item "*Is this event related to Nivolumab?*" ticked "*Yes*" in "*Adverse Event*" form of the eCRF. If the data is missing, the AE will be considered as related to Nivolumab.

AEs related to IMP (Pexa-Vec + Nivolumab)

AEs related to IMP are the AEs related to either Pexa-Vec or Nivolumab (or both).

AE leading to treatment discontinuation

AE leading to discontinuation are the AEs with the items "*Action taken with Pexa-Vec*" or "*Action taken with Nivolumab*" ticked "*Drug withdrawn*".

Immune-related AEs

Immune-related AEs are the AEs with the item "*Is this event immune related ?*" ticked "*Yes*".

AE leading to death

The AE leading to death are the AEs with the item

- "*Toxicity grade*" ticked "*Grade 5 or Fatal*" or

- "*Outcome*" ticked "*Fatal*"

8.8.1.3 Listings

All AEs will be listed with the following items:

- Patient Number
- Cohort (Cohort #1 and Cohort #-1)
- Age / Gender
- Verbatim, PT and SOC
- Date of onset and date of end (study day)
- Duration of the AE in days
- Toxicity grade (Grade 1 / Grade 2 / Grade 3 / Grade 4 / Grade 5)
- Outcome (Recovered / Recovered with sequelae / Not recovered / Fatal / Unknown)
- Relation to Pexa-Vec (Related/Not Related) and Action taken regarding Pexa-Vec
- Relation to Nivolumab (Related/Not Related) and Action taken regarding Nivolumab
- Relation to Study Procedure (Related/Not Related)
- Action regarding the event (None / Medication given / Procedure implemented/Early study termination/ Required Hospitalization)
- Evaluation of seriousness
- Dose-limiting toxicity (Y/N)
- Event immune related (Y/N)
- AE subject to immediate reporting
- DLT population flag (Y/N)
- PP population flag (Y/N)

Moreover, the following sub-listings will be provided:

- AEs subject to immediate reporting
- Dose-limiting toxicity AEs
- IMP-related AEs

- Immune-related AEs
- SAEs
- IMP-related SAEs
- AEs leading to treatment discontinuation
- Grade 3/4/5 adverse events
- Fatal AEs

8.8.1.4 Tables

An overview table will be presented by Cohort (Cohort#1, Cohort#-1 and overall) with the number and percentage of patients for each of the following categories (the number of events will be also provided) with at least:

- one AE
- one AE subject to immediate reporting
- one dose limiting toxicity AEs
- one immune-related AEs
- one AEs related to IMP
- one AEs related to Pexa-Vec
- one AEs related to Nivolumab
- one AEs related to study procedure
- one AEs leading to treatment discontinuation
- one AEs related to IMP and leading to treatment discontinuation
- one SAE
- one SAEs related to IMP
- one grade 3/4/5 AEs
- one grade 3/4/5 AEs related to IMP
- one grade 3/4/5 AEs related to IMP leading to treatment discontinuation

The number and percentage of patients for each category above will be summarized by Cohort (Cohort#1, Cohort#-1 and overall) in a frequency table by body system organ class (SOC) and preferred terms (PT) as per MedDRA dictionary. The number of events will be also summarized in the same table.

Table for AEs, AEs related to IMP, AEs related to Pexa-Vec and AEs related to Nivolumab will also be presented by grade and summarized by Cohort (Cohort#1, Cohort#-1 and overall) in a frequency table by SOC and PT as per MedDRA dictionary.

8.8.2 Laboratory abnormalities

Listings of laboratory data will be provided by visit and displaying the Standard International (SI) units converted laboratory parameters with at least value, change from baseline, reference range, high/low, grade (if applicable) and clinical significance.

Laboratory data will be summarized at baseline by presenting descriptive statistics for all hematology and biochemistry parameters. All values will be displayed in SI units. A dedicated listing will be done for AFP results (reported in ng/mL).

Laboratory parameters (hematology and biochemistry) will be graded using the NCI-CTCAE version 4.03, dated June 14, 2010. A shift table of baseline CTCAE grade versus worst CTCAE grade during study will be presented for hematology and biochemistry parameters by Cohort (Cohort#1, Cohort#-1 and overall). For parameters with two directions abnormalities (decrease/increase), two shift tables will be presented. The list of laboratory parameters and their abnormalities graded according to CTCAE are presented in section 11.

8.8.3 Other safety data

Vital signs collected during and up to 24h after IMP administration

All vital signs collected during and up to 24h after IMP administration (either Pexa-Vec or Nivolumab) will be listed for each patient and visit administration.

Vital signs and physical examinations

All vital signs (SBP and DBP in mmHg, heart rate in bpm, respiratory rate in bpm, temperature in °C, body weight in kg and BMI in kg/m²) and physical examinations will be listed by patients. All these results will be presented for SAF and DLT populations for Phase I and for SAF population for Phase IIa by cohort.

Thyroid function

Thyroid function will be listed by patients. All these results will be presented for SAF and DLT populations for Phase I and for SAF population for Phase IIa by cohort.

ECOG

ECOG performance status will be listed by patients. All these results will be presented for SAF and DLT populations for Phase I and for SAF population for Phase IIa by cohort.

Electrocardiogram, echocardiogram and Troponin levels

All electrocardiogram results performed during the study will be listed for SAF population (all abnormalities will be listed).

Results of echocardiogram (Left Ventricular Ejection Fraction expressed in percentage) and Troponin levels (Troponin I and Troponin T, expressed in ng/mL) will be listed together for SAF population. Results of echocardiogram will be presented with abnormalities details.

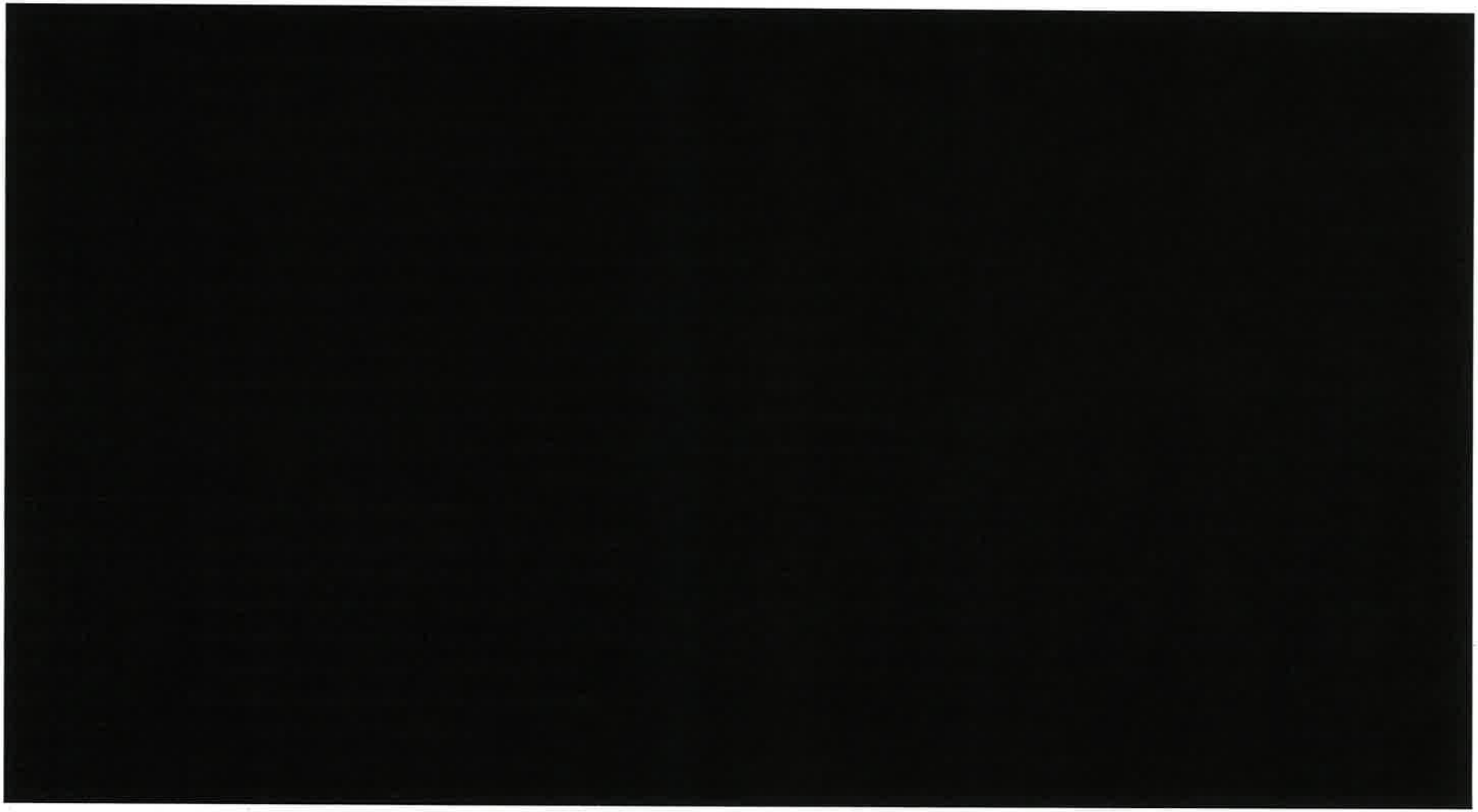
9 CHANGE HISTORY

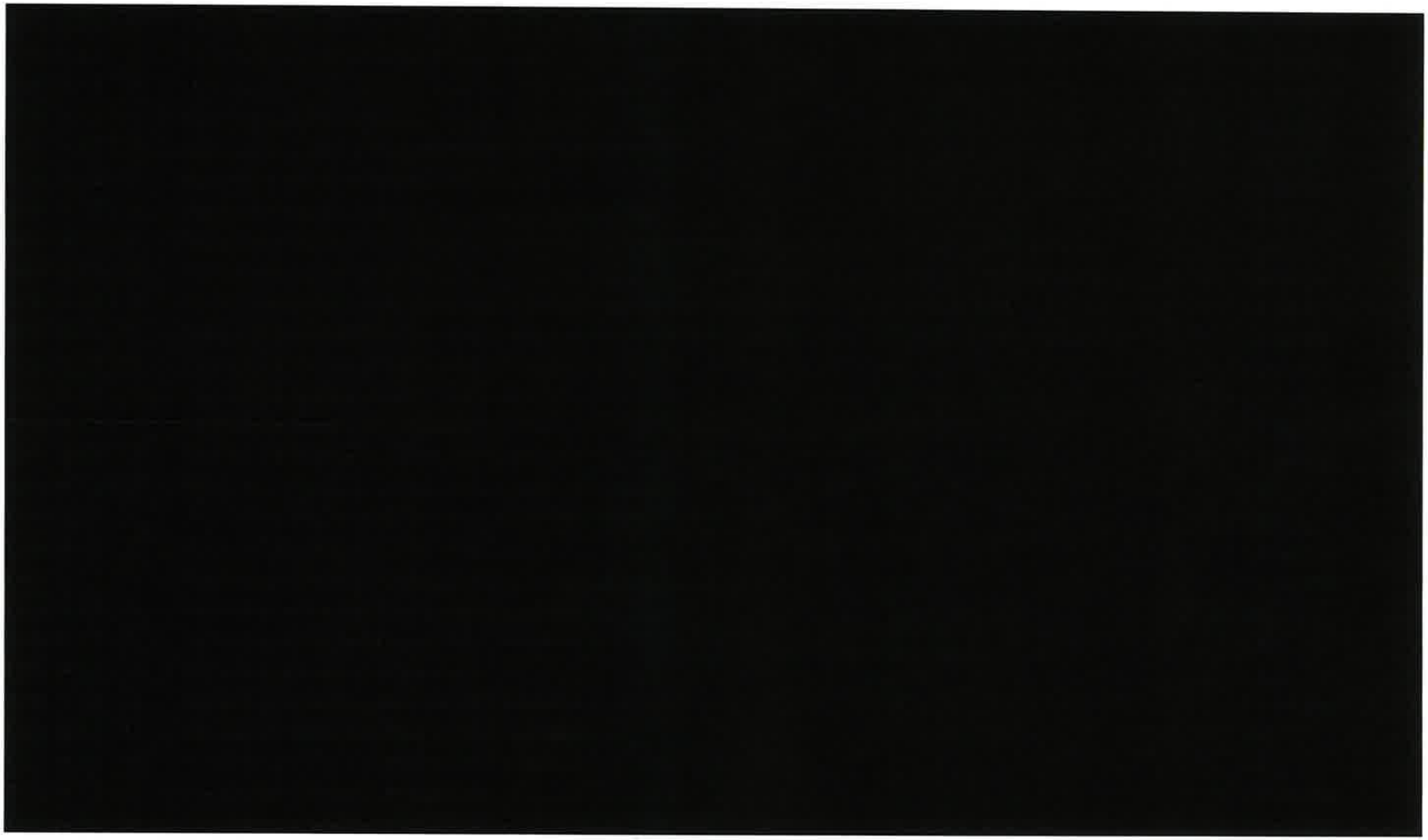
- Version 2 (dated 09 May 2018): Update of TFL to match ICH standard, removal of laboratory summary tables over time and new definitions for derived variables (First treatment administration as baseline value). Listing and tables for AEs subject to immediate reporting added following protocol version dated 22 December 2017.

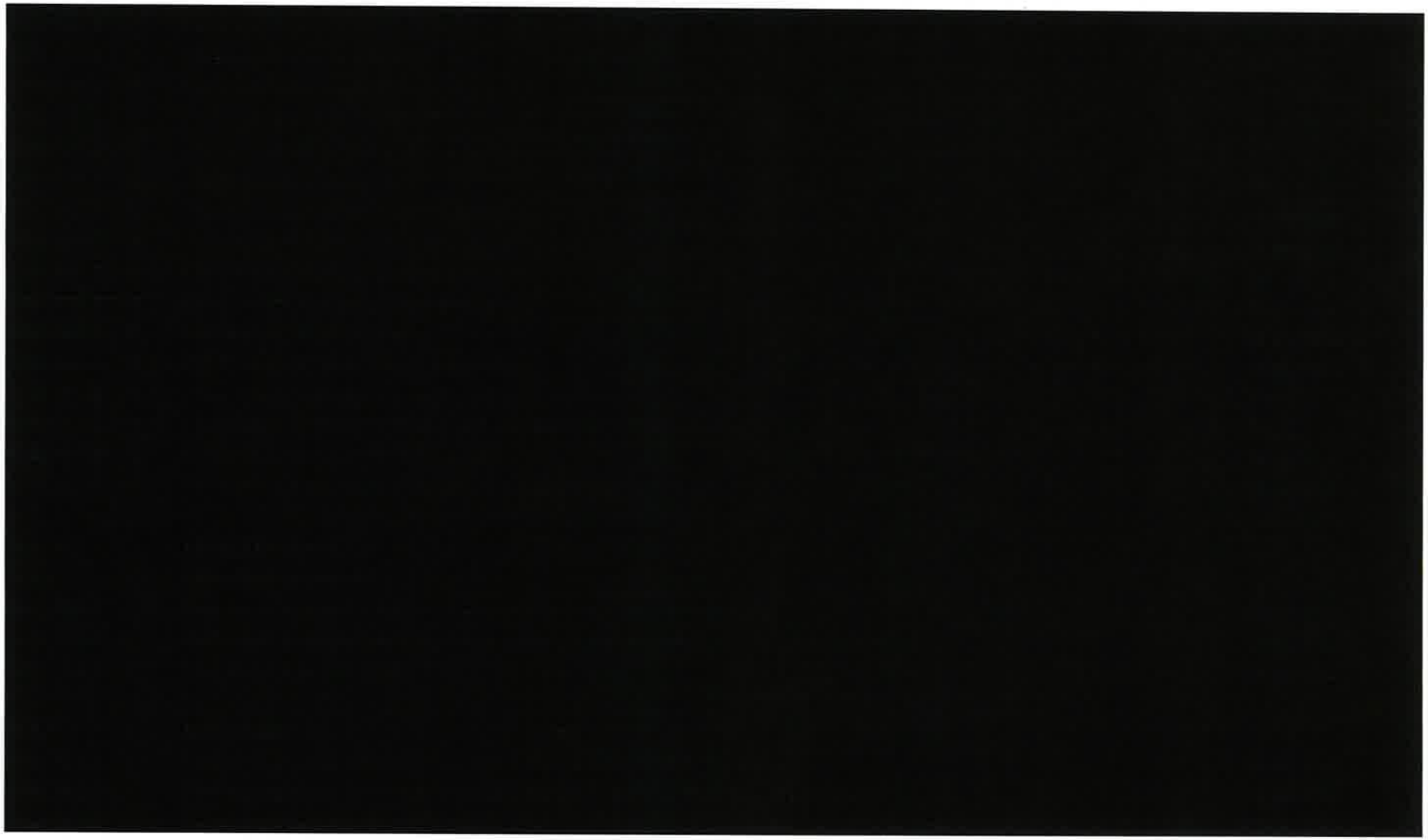
- Version 3 (dated 12 December 2018): Addition of AFP listing (separated from urinalysis results) and listing for echocardiogram and Troponin level. Modification of treatment compliance definitions. Addition of imputation rules for partial birthdates if day is missing. Addition of rules for laboratory parameters intensity grade when normal limits are missing and addition of laboratory parameters to be graded according to CTCAE V4.03. Deletion of the listing of eligibility criteria for enrolled patients because of duplication with listing of protocol deviation at inclusion for enrolled patients. Deletion of tables of other safety data (vital signs, thyroid function, ECOG and ECG). Addition of listings with reason for exclusion from DLT population and PP population. Addition of formulas of calculated creatinine clearance (Cockcroft-Gault formula) and corrected calcium.

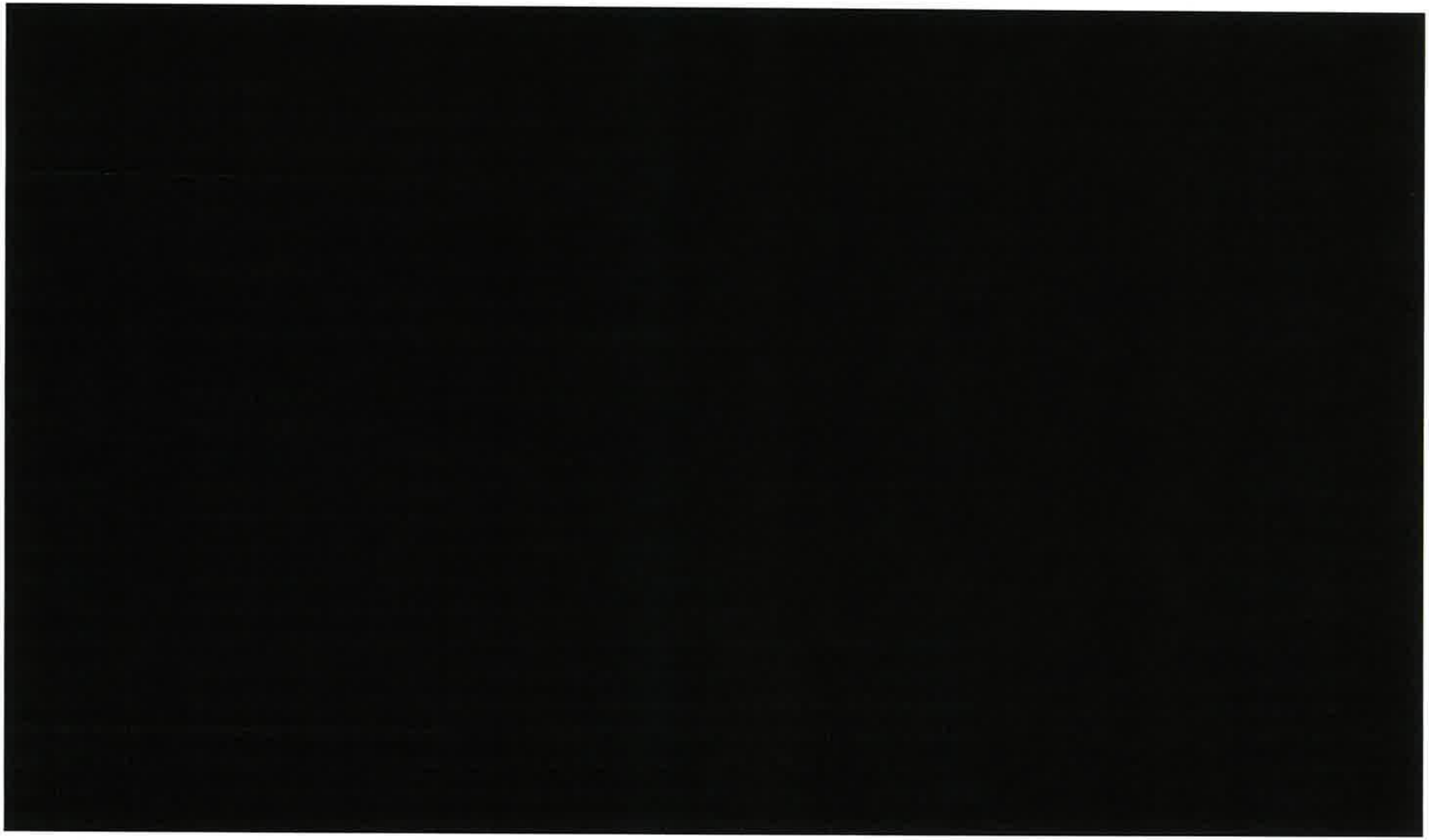
10 LIST OF TABLES, FIGURES AND LISTINGS

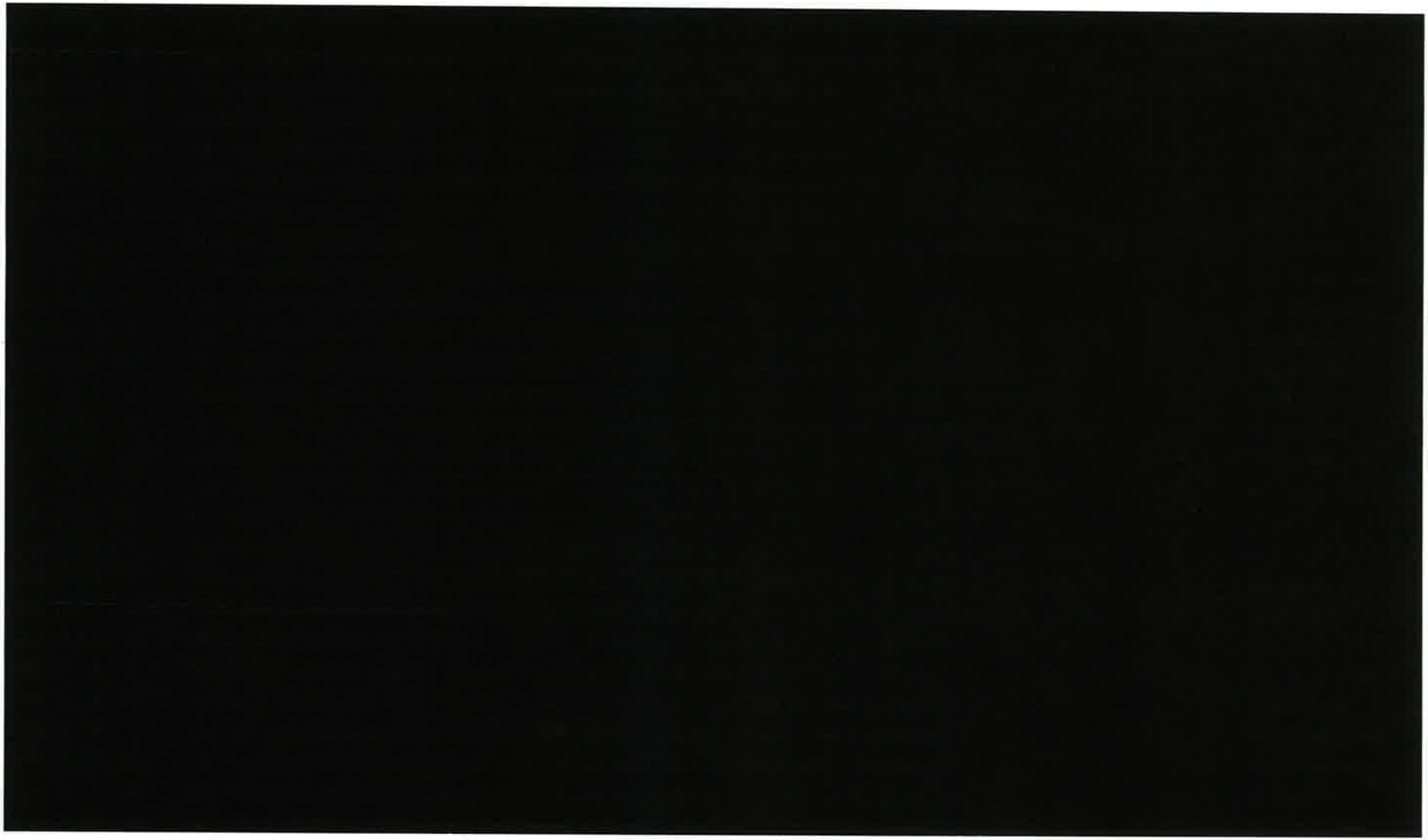
10.1 TABLES

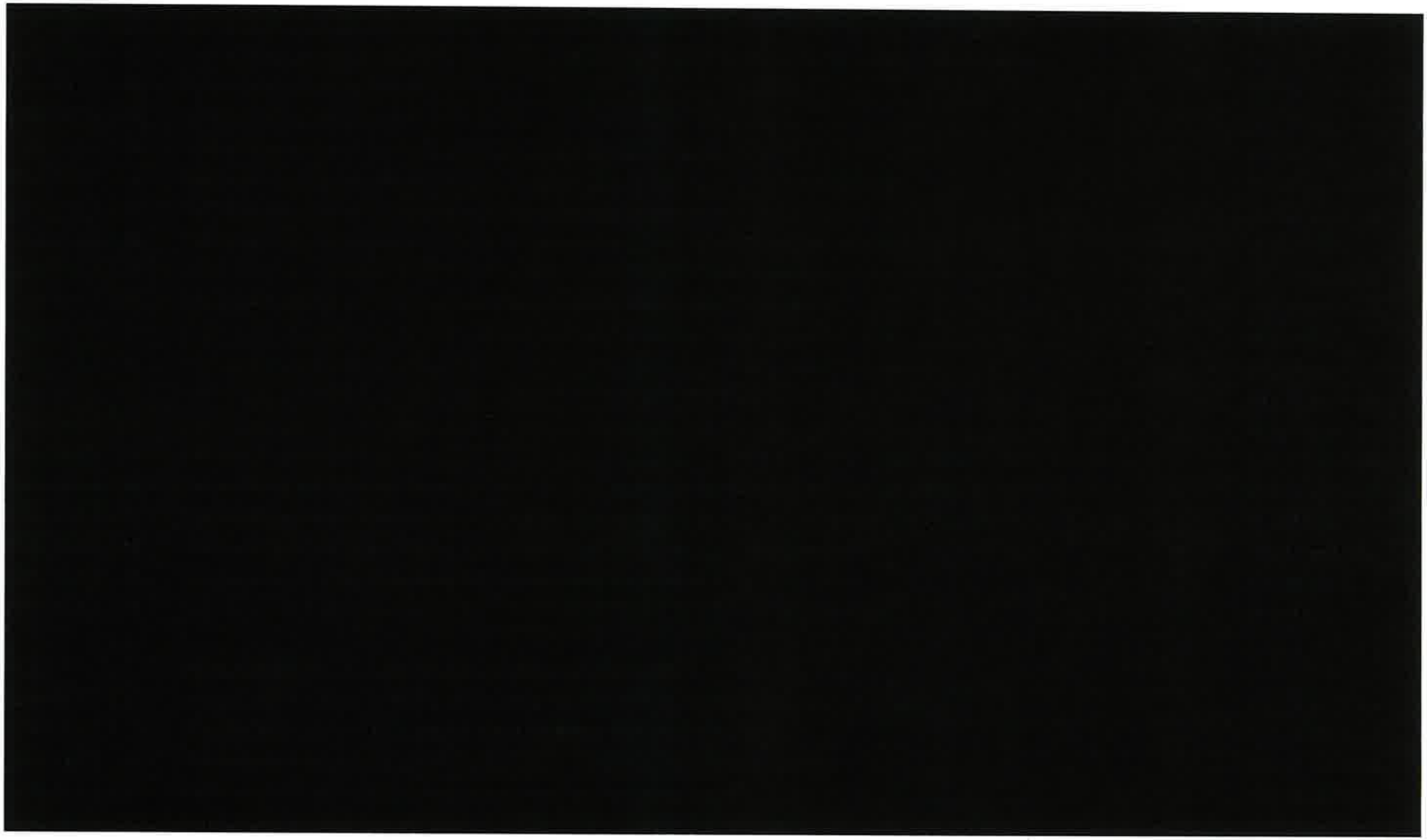


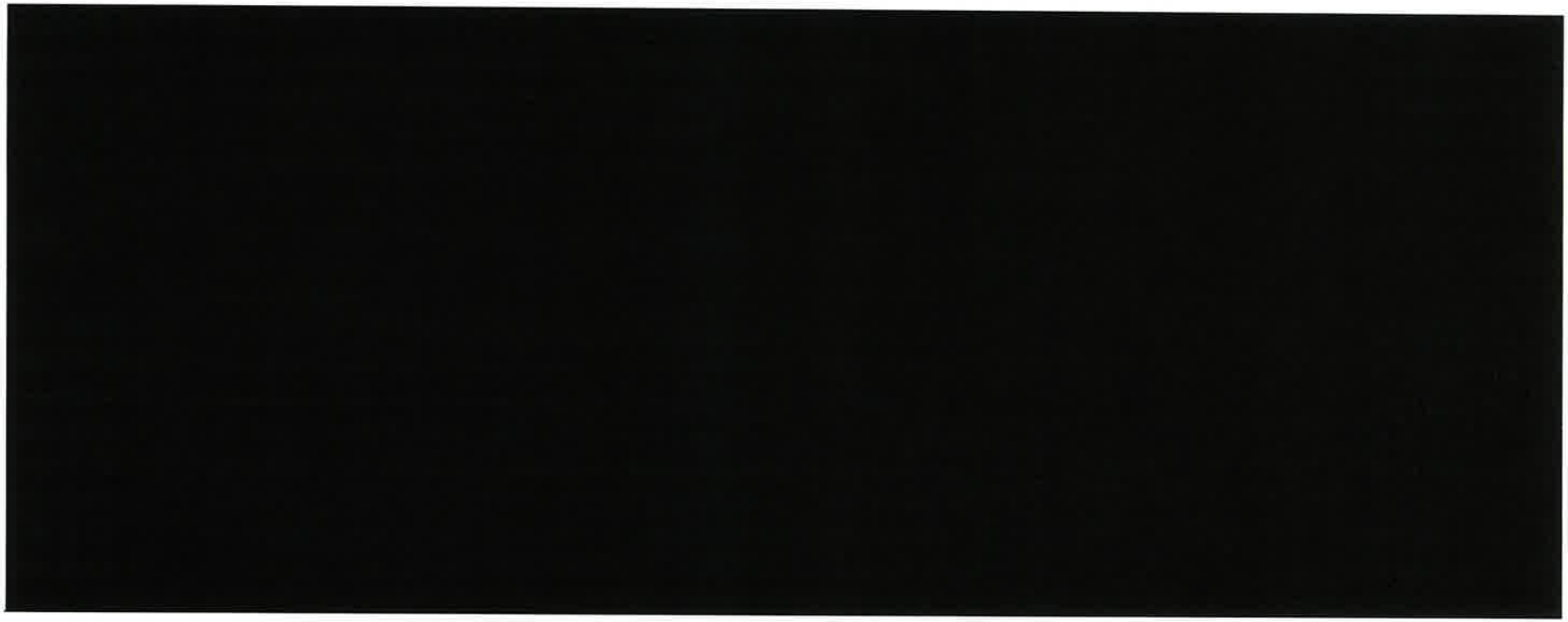




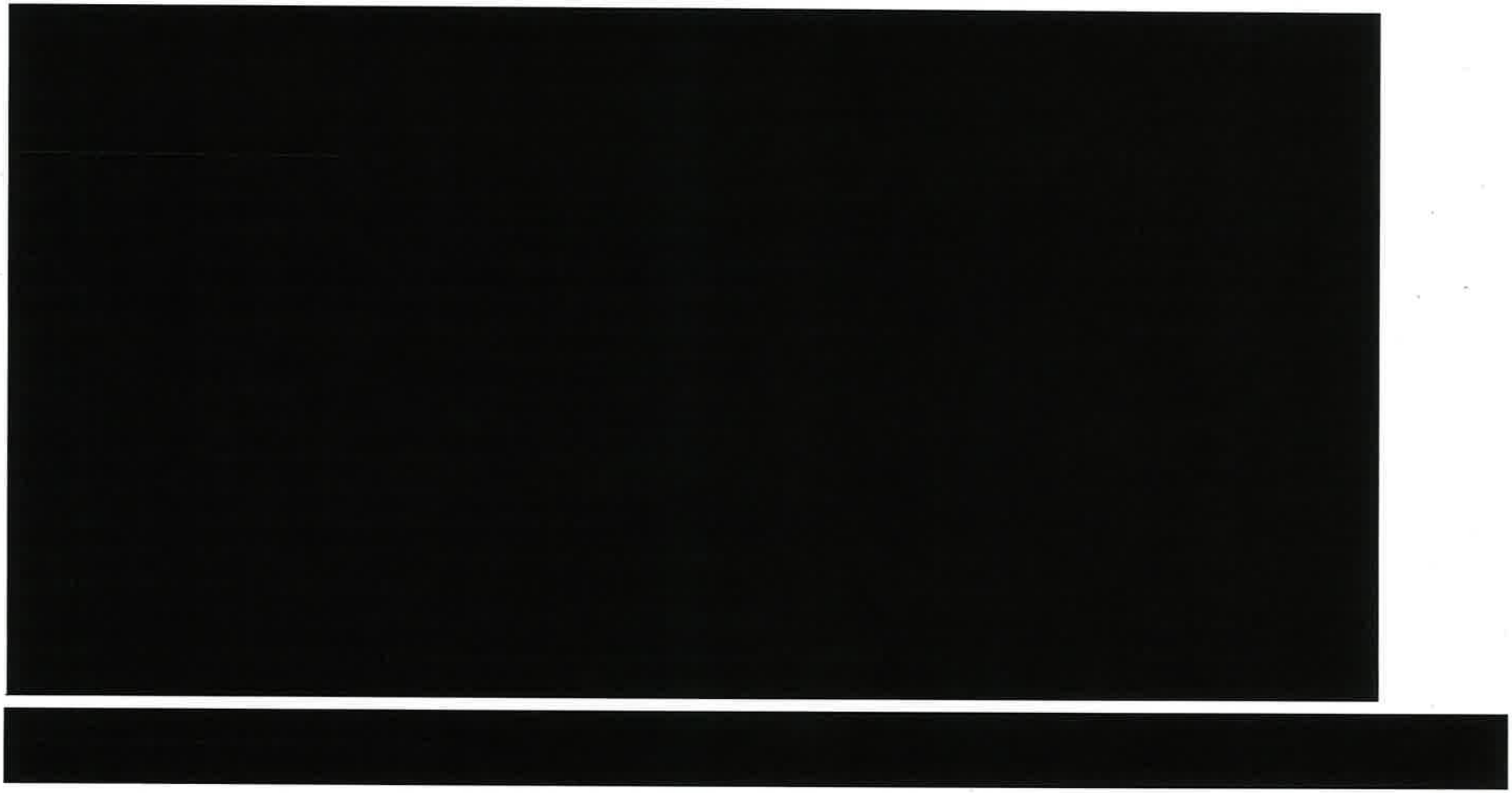




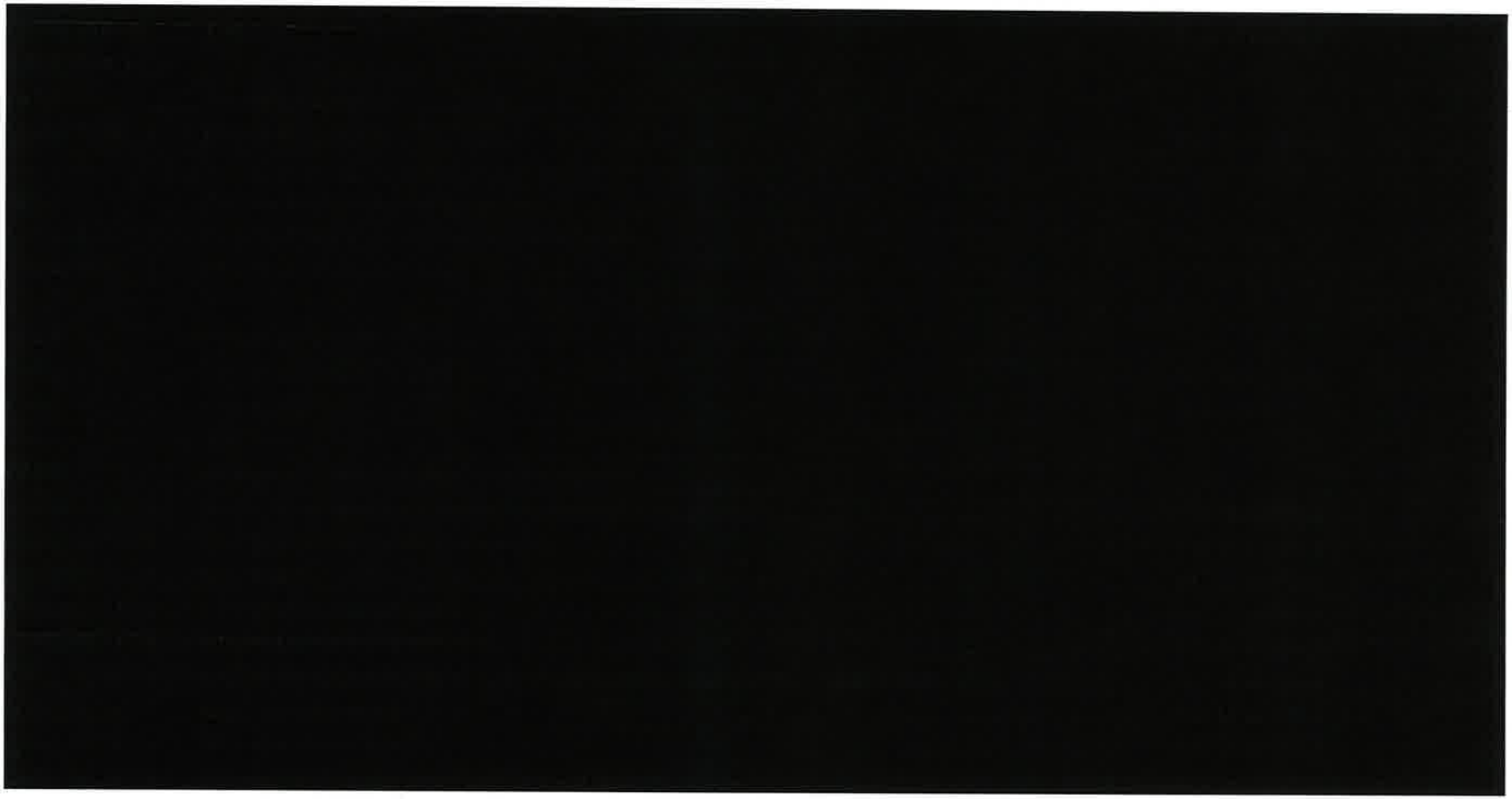


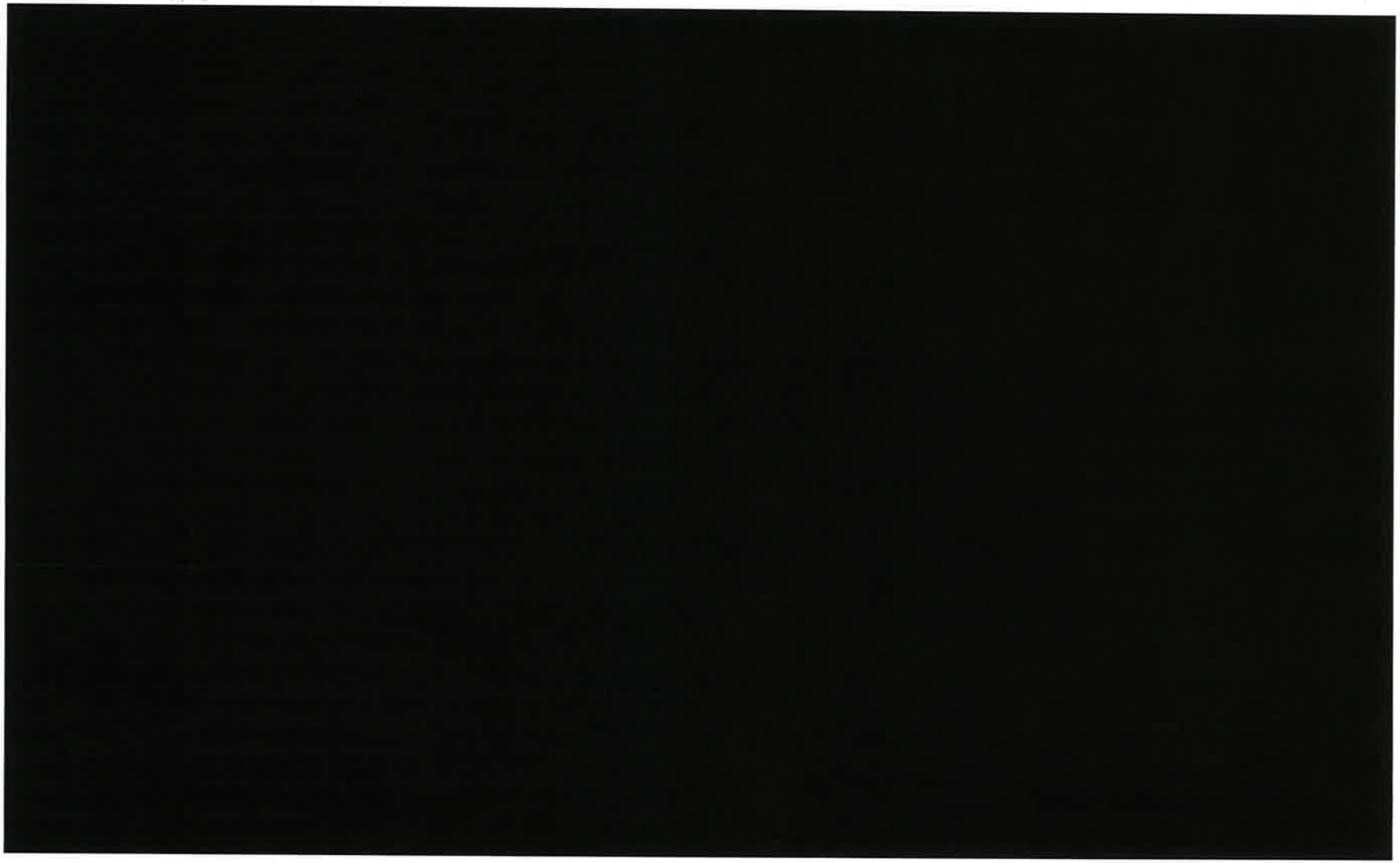


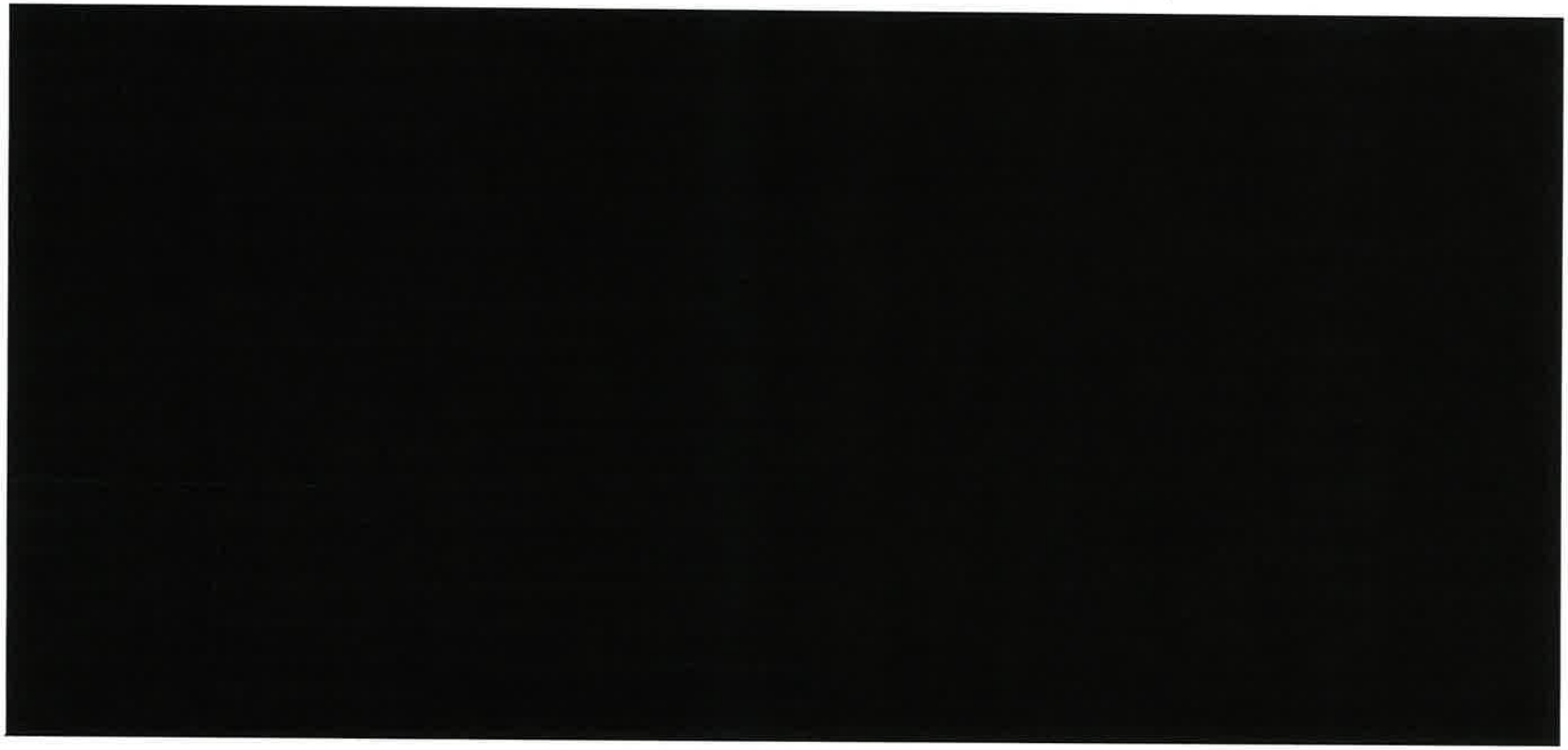
10.2 FIGURES



10.3 LISTINGS







11 APPENDIX 1 – COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.03 (CTCAE)

In the tables below, Grade 5 corresponding to death was not detailed.

Lab Test Name	SI Unit	CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	g/L	Investigations	Hemoglobin increased	Increase in >0 - 20 g/L above ULN	Increase in >20 - 40 g/L above ULN	Increase in >40 g/L above ULN	--
Hemoglobin	g/L	Blood and lymphatic system disorders	Anemia	<LLN - 100 g/L	<100 - 80g/L	<80 g/L	Life-threatening consequences
Leukocytes	10^9/L	Investigations	White blood cell decreased	<LLN - 3.0 x 10^9/L	<3.0 - 2.0 x 10^9/L	<2.0 - 1.0 x 10^9 /L	<1.0 x 10^9/L
Leukocytes	10^9/L	Blood and lymphatic system disorders	Leukocytosis			> 100 x 10^9 /L	Clinical manifestations of leucostasis; urgent intervention indicated
Platelets	10^9/L	Investigations	Platelet count decreased	<LLN - 75.0 x 10^9/L	<75.0 - 50.0 x 10^9/L	<50.0 - 25.0 x 10^9/L	<25.0 x 10^9/L
Neutrophils	10^9/L	Investigations	Neutrophil count decreased	<LLN - 1.5 x 10^9/L	<1.5 - 1.0 x 10^9/L	<1.0 - 0.5 x 10^9/L	<0.5 x 10^9/L
Lymphocytes	10^9/L	Investigations	Lymphocyte count decreased	<LLN - 0.8 x10^9 /L	<0.8 - 0.5 x 10^9 /L	<0.5 - 0.2 x 10^9 /L	<0.2 x 10^9 /L
Lymphocytes	10^9/L	Investigations	Lymphocyte count increased	--	>4x10^9/L – 20*10^9/L	>20*10^9/L	--

Sodium	mmol/L	Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	--	<130 - 120 mmol/L	<120 mmol/L

Lab Test Name	SI Unit	CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Sodium	mmol/L	Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Magnesium	mmol/L	Metabolism and nutrition disorders	Hypomagnesemia	>ULN - 1.23 mmol/L	--	>1.23 - 3.30 mmol/L	>3.30 mmol/L
Magnesium	mmol/L	Metabolism and nutrition disorders	Hypermagnesemia	<LLN - 0.5 mmol/L	<0.5 - 0.4 mmol/L	<0.4 - 0.3 mmol/L	<0.3 mmol/L
Phosphate	mmol/L	Metabolism and nutrition disorders	Hypophosphatemia	<LLN - 0.8 mmol/L	<0.8 - 0.6 mmol/L	<0.6 - 0.3 mmol/L	<0.3 mmol/L
Potassium	mmol/L	Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	--	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Potassium	mmol/L	Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Creatinine	umol/L	Investigations	Creatinine increased	>ULN - 1.5 x ULN; >1 - 1.5 x baseline	>1.5 - 3.0 x ULN; >1.5- 3.0 x baseline	>3.0 - 6.0 x ULN; >3.0 baseline	>6.0 x ULN
Glucose	mmol/L	Metabolism and nutrition disorders	Hypoglycemia	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L

Glucose	mmol/L	Metabolism and nutrition disorders	Hyperglycemia	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Bilirubin	µmol/L	Investigations	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Alanine Aminotransferase	U/L	Investigations	Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate Aminotransferase	U/L	Investigations	Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkaline Phosphatase	U/L	Investigations	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

Lab Test Name	**SI Unit**	**CTCAE v4.03 SOC**	**CTCAE v4.03 Term**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Corrected Calcium	mmol/L	Metabolism and nutrition disorders	Hypocalcemia	<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L	<1.75 - 1.5 mmol/L	<1.5 mmol/L
Corrected Calcium	mmol/L	Metabolism and nutrition disorders	Hypercalcemia	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L	>3.1 - 3.4 mmol/L	>3.4 mmol/L
Albumin	g/L	Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 30 g/L	<30 - 20 g/L	<20 g/L	--
APTT	s	Investigations	Activated partial thromboplastin time	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	--

			prolonged				
Prothrombin Intl. Normalized Ratio		Investigations	INR increased	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	--