NCT03367819

STATISTICAL ANALYSIS PLAN

COMPOUND: isatuximab/SAR650984

A Phase 1/2 open-label, multi-center, safety, preliminary efficacy and pharmacokinetic (PK) study of isatuximab (SAR650984) in combination with REGN2810 or isatuximab alone in patients with advanced malignancies

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibodies
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANC:	absolute neutrophils count
aPTT:	activated partial thromboplastin time
AST:	aspartate aminotransferase
ATC:	anatomic therapeutic category
AUC:	area under the curve
BOR:	best overall response
BUN:	blood urea nitrogen
CD38:	cluster of differentiation 38
CR:	complete response
CTCAE:	common terminology criteria for adverse events
DCR:	disease control rate
DL-1:	dose level minus 1
DLT:	dose limiting toxicity
DOR:	duration of response
ECG:	electorcardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
EOT:	end of treatment
FCGR:	fc gamma receptor
IAR:	infusion associated reaction
IMP:	investigational medicinal product
INR:	international normalized ratio
iRECIST:	modified response evaluation criteria in solid tumors for immune based therapies
IV:	intravenous
LDH:	lactate dehydrogenase
mCRPC:	metastatic, castration resistant prostate cancer
MDRD:	modified diet in renal disease
MedDRA:	medical dictionary for regulatory activities
MTD:	maximum tolerated dose
NCI:	National Cancer Institute, National Cancer Institute
NIMP:	non-investigational medicinal product
NSCLC:	non-small cell lung cancer
OS:	overall survival
PCSA:	potentially clinically significant abnormality
PCWG3:	prostate cancer clinical trials working group 3
PD:	progressive disease

PD-1:	programmed cell death 1
PD-L1:	programmed cell death-ligand
PFS:	progression-free survival
PK/PD:	pharmacokinetics/pharmacodynamics
PR:	partial response
PSA:	prostate-specific antigen
PT:	preferred term
PTT:	partial thromboplastin time
RBC:	red blood cell
RECIST:	response evaluation criteria in solid tumors
ROI:	region of interest
RP2D:	recommended phase 2 dose
rPFS:	radiographic progression-free survival
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	stable disease
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TSH:	thyroid stimulating hormone
WBC:	white blood cells
WHO-DD:	World Health Organization-Drug Dictionnary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN

This is an open-label, multi-center, non-comparative, Phase 1/2 study to evaluate the safety, preliminary efficacy and PK of isatuximab in combination with REGN2810 (cemiplimab) or isatuximab alone in patients with advanced malignancies.

The study will be conducted in up to 3 parts:

- The Phase 1 part (safety run-in) is to characterize the safety and tolerability of isatuximab in combination with REGN2810 and to confirm the recommended phase 2 dose (RP2D)
- The Phase 2 part (efficacy signal search with Simon's 2-stage design) is to assess the preliminary efficacy of isatuximab in combination with REGN2810 or isatuximab alone
- Cross-over part (a subpart of Cohort A-2) in which patients who progress on isatuximab monotherapy may receive isatuximab plus REGN2810 if they still fulfill the eligibility criteria (except exclusion criteria #3 and #8)

Isatuximab and REGN2810 are defined in this protocol as "study treatments".

1.1.1 Phase 1 part (safety run-in)

Patients with either metastatic, castration resistant prostate cancer (mCRPC) or non-small cell lung cancer (NSCLC) will be enrolled in the Phase 1 part. There is no minimum patient number requirement for either tumor type.

1.1.1.1 Starting dose and de-escalation design

The starting dose is selected based on past and ongoing clinical trials. Starting dose is 350 mg Q3W for REGN2810 with isatuximab given 10 mg/kg QW for 3 weeks followed by Q3W. Dose de-escalation will be performed if necessary as defined in Table 1 below:

Table 1 - Dose modification for Phase 1

Dose level	Isatuximab	REGN2810
Starting dose	10 mg/kg QW × 3->Q3W	350 mg Q3W
Minus 1 (DL-1)	5 mg/kg QW × 3->Q3W	350 mg Q3W

Abbreviations: DL=dose level; QW=once weekly; Q3W=once every 3 weeks.

At the starting dose, dose limiting toxicity (DLT) will be assessed in the first 6 patients (1 cycle; 21 days):

- If ≤1/6 patient has DLT, the starting dose will be the RP2D
- If 2/6 patients have DLT, 6 additional patients will be enrolled at starting dose level:
  - If a total of 2/12 patients treated at starting dose have DLT, starting dose will be the RP2D
  - If a total of ≥3/12 patients have DLT, dose will be de-escalated to dose level minus 1 (DL-1)
- If ≥3/6 patients have DLT, dose will be de-escalated to DL-1

An additional 6 patients may be enrolled at DL-1; if ≤1/6 patient has DLT, DL-1 will be the RP2D. At DL-1, if ≥2/6 patients have DLT, an alternative dose/schedule might be considered from a safety viewpoint by the Sponsor after consulting with the Investigators who recruit patients for the Phase 1 part.

The DLT observation period is 1 cycle (21 days). The duration of the DLT observation period will be longer for patients who delay initiation of Cycle 2 due to treatment-related adverse event (AE) for which the duration must be assessed in order to determine if the event is a DLT. All AEs during treatment, unless due to disease progression or an obviously unrelated cause, will be taken into consideration by the Sponsor and recruiting Investigators for the determination of the maximum tolerated dose (MTD) and RP2D.

Investigational medicinal product (IMP) initiation of patients in the Phase 1 part is to be staggered by ≥3 days. The National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 4.03 will be used to assess the severity of AEs. Causal relationship is to be determined by the Investigator. The DLTs will be confirmed by the Sponsor and recruiting Investigators.

1.1.1.2 Maximum tolerated dose

The MTD is defined as the highest dose level at which no more than 1 out of 6 patients (starting dose or DL-1) or 2 out of 12 patients (starting dose) experience an IMP related DLT. The RP2D is defined as the dose selected for the Phase 2 portion.

1.1.2 Phase 2 part (efficacy signal)

The Phase 2 part may include up to 5 cohorts:

- Cohort A-1: mCRPC, isatuximab and REGN2810 combination therapy
- Cohort A-2: mCRPC, isatuximab monotherapy
- Cohort B: NSCLC, isatuximab and REGN2810 combination therapy
- Possibly Cohort C: mCRPC, isatuximab and REGN2810 combination therapy, or isatuximab monotherapy without initial isatuximab weekly dosing
- Possibly Cohort D: NSCLC, isatuximab and REGN2810 combination therapy without initial isatuximab weekly dosing

Enrollment in Cohort A-2 will start only if the decision to proceed to Phase 2 Stage 2 in Cohort A-1 is made.

The patients treated at the RP2D of isatuximab and REGN2810 in combination during Phase 1 will be included in the efficacy analysis together with patients of the same tumor type in Stage 1 of Phase 2. Based on the number of objective responses (observed up to 6 cycles after the last ongoing patient receives first dose of IMP) and the totality of data observed within a treatment cohort in Phase 2 Stage 1, the Sponsor may decide to advance such a treatment cohort to Phase 2 Stage 2 after consulting with Investigators. After enrollment completion of Phase 2 Stage 1, if efficacy results do not warrant initiation of Stage 2, enrolment will be paused until sufficient results or analyses warrant initiation of Phase 2 Stage 2.

For patients with mCRPC, if it is decided to run Phase 2 Stage 2, an isatuximab monotherapy cohort will be initiated for this population (Cohort A-2); patients with mCRPC will be randomly assigned in a 1:1 randomization ratio to enter Cohort A-1, isatuximab and REGN2810 combination (Phase 2 Stage 2) or Cohort A-2, isatuximab monotherapy (Phase 2 Stage 1). The isatuximab single agent dose and schedule for cohort A-2 is 10 mg/kg QW for 3 weeks followed by Q3W.

Based on the efficacy signal and the totality of data observed within a tumor type at end of Phase 2 Stage 2, the Sponsor may decide to further study isatuximab 10 mg/kg Q3W in combination with REGN2810 or isatuximab 10 mg/kg Q3W as a monotherapy in patients with mCRPC (Cohort C) or isatuximab 10 mg/kg Q3W in combination with REGN2810 in patients with NSCLC (Cohort D), without the isatuximab doses of 10 mg/kg QW for 3 weeks. The schedule without the initial weekly dosing may be more practical for patients and health care providers. Objectives and study design considerations for Cohort C and Cohort D are the same as those for other cohorts in the same tumor type. The Sponsor may decide to test an isatuximab dose of 20 mg/kg in case of inadequate efficacy and PK results.

1.1.3 Cross-over part (a subpart of cohort A-2)

Patients from Cohort A-2 who progress on isatuximab monotherapy may receive isatuximab plus REGN2810 at the discretion of the Investigators and if they still fulfill the eligibility criteria (except exclusion criteria #3 and #8). The screening period for the cross-over part is 28 days from progressive disease (PD) confirmation.

All screening processes for the patients in the Phase 1 and Phase 2 parts are to be conducted before combination IMP initiation for the cross-over part, except informed consent, demography, medical/surgical and disease history, and weight/height. Tumor biopsy at cross-over screening is required unless clinically unfeasible and after discussion with the Sanofi Medical Monitor. On treatment biopsy at Cycle 2, Day 1 (±7 days) of the cross-over part is optional (fine needle aspirate is not acceptable). Patients who are included in the cross-over part should be evaluated as Cohort A-1 and Cohort B (except PK).

Patients who do not meet the cross-over part eligibility criteria should be followed up for safety and survival.

1.2 OBJECTIVES

1.2.1 Primary objectives

Phase 1:

- To characterize the safety and tolerability of isatuximab in combination with REGN2810 in patients with mCRPC who are naïve to anti-programmed cell death 1 (PD-1)/programmed cell death-ligand (PD-L1)-containing therapy naive, or NSCLC who progressed on anti-PD-1/PD-L1-containing therapy, and to confirm the RP2D

Phase 2 (applicable to Cohorts A-1, A-2, B, C, and D):

- To assess the RR of isatuximab in combination with REGN2810 in patients with either mCRPC who are anti-PD-1/PD-L1 therapy naive, or NSCLC who progressed on anti-PD-1/PD-L1 therapy, **or** of isatuximab as single agent in patients with mCRPC

1.2.2 Secondary objectives

- To evaluate the safety of the combination of isatuximab with REGN2810 or isatuximab monotherapy
- To evaluate the immunogenicity of isatuximab and REGN2810
- To characterize the PK profile of isatuximab single agent or in combination with REGN2810, and to characterize the PK of REGN2810 in combination with isatuximab
- To assess overall efficacy of isatuximab in combination with REGN2810 or single agent (tumor burden change, duration of response [DOR], and progression-free survival [PFS])

1.3 DETERMINATION OF SAMPLE SIZE

Phase 1

In Phase 1, approximately 6 (assuming 6 patients for the starting dose) to 24 (assuming 12 patients for the starting dose plus 12 patients for DL-1) DLT evaluable patients are expected to be enrolled. The actual sample size will vary depending on DLTs observed and the number of dose levels explored. Patients who are not evaluable for DLT assessment in the Phase 1 part may be replaced.

Phase 2

The Phase 2 part of the study is to evaluate initial anti-tumor activity based on tumor response using response evaluation criteria in solid tumors (RECIST) 1.1 criteria (1) for NSCLC and prostate cancer clinical trials working group 3 (PCWG3) criteria (2) for mCRPC. The efficacy evaluation is based on Simon's 2 stage designs with 90% power at 5% 1-sided alpha level for each of the patient cohorts of mCRPC and NSCLC patients, respectively. The assumption of RR, the required sample sizes and the number of responders at each stage are provided in Table 2.

Table 2 - Sample size calculation

Indication	H0	H1	Sample size		Number (%) of required responses	
			Stage 1	Final	Stage 1	Final
mCRPC (Combo)	10%	26%	23	49	≥3 (13.0%)	≥9 (18.4%)
mCRPC (Single)	10%	26%	20	36	≥2 (10.0%)	≥5 (13.9%)
NSCLC (Combo)	5%	22%	20	36	≥2 (10.0%)	≥5 (13.9%)

Abbreviations: H0=null hypothesis; H1=alternative hypothesis; mCRPC=metastatic, castration-resistant prostate cancer; NSCLC=non-small cell lung cancer.

Note: Based on the number of objective responses and the totality of data observed within a treatment cohort in Phase 2 Stage 1, the Sponsor may decide to advance such a treatment cohort to Phase 2 Stage 2 after consulting with Investigators.

Patients who received the recommended dose regimen in Phase 1 will be also included in the Phase 2 Stage 1 (eg, if 6 NSCLC patients were enrolled in Phase 1, only 14 NSCLC patients will be needed to complete the Phase 2 Stage 1 NSCLC cohort).

In Phase 2, approximately 134 patients are expected to be enrolled (assuming Cohort A-1, A-2 and B complete 2 stages), including approximately 66 patients in Phase 2 Stage 1 and approximately 68 patients in Phase 2 Stage 2. The patients who are treated with RP2D in the Phase 1 part will be counted as Phase 2 part patients. If isatuximab 10 mg/kg Q3W in combination with REGN2810 or monotherapy without the isatuximab 10 mg/kg QW for 3 weeks is to be tested in a mCRPC or NSCLC cohort, 49 or 36 additional patients will be needed, respectively.

The isatuximab monotherapy cohort (Cohort A-2) will be initiated when the initial anti-tumor activity of isatuximab combination therapy is observed in the Phase 2 Stage 1 according to the study design. When an isatuximab monotherapy cohort (Cohort A-2) is initiated, patients with mCRPC will be randomly assigned in a 1:1 randomization to either the isatuximab in combination with REGN2810 (Cohort A-1) or the isatuximab monotherapy (Cohort A-2). The purpose of the randomization is to avoid the potential bias of patient assignment, and is not to compare between 2 cohorts. Randomization will end when 1 of the 2 cohorts completes the enrollment.

1.4 STUDY PLAN

The complete study plan is presented in section 1.1 of the protocol.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Not applicable.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable. This is not an amended statistical analysis plan (SAP).

2 STATISTICAL AND ANALYTICAL PROCEDURES

Patients treated at the RP2D in Phase 1 will be included in the analysis with patients of the same tumor type in Phase 2. If the RP2D is the starting dose, all data from the patients in phase 1 will be summarized together with the data from the patients of the same tumor type in Phase 2 except for the DLT analysis.

Data from mCRPC and NSCLC cohorts in the Phase 2 part will be analyzed and reported separately by cohort. Data from the cohort A-2 cross-over part will be summarized separately unless otherwise noted.

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last assessment for this parameter before first administration of study treatments unless otherwise noted.

All baseline safety and efficacy parameters (apart from those listed below) will be presented along with summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.6).

Demographic characteristics

Demographic variables include race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown), age in years, weight (kg), height (cm) and eastern cooperative oncology group (ECOG) performance status at baseline.

Medical or surgical history

Medical or surgical history includes relevant history of previous or associated pathologies other than the tumor.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at diagnosis

The following disease characteristics at initial diagnosis will be described:

- Time from initial diagnosis to first study treatment administration (in years)
- Histology (diagnosis as collected in electronic case report form (eCRF))
- Disease Location
- Histopathology type (as collected in eCRF)

- Stage of the disease (as collected in eCRF)
- Gleason Score (for patients with mCRPC)

Disease characteristics at study entry - mCRPC

The following disease characteristics at study entry will be described:

- Disease extent (metastatic, Loco Regional Recurrence, Primary, locally advanced)
- Criteria for progression (prostate-specific antigen (PSA), soft tissue, bone metastasis)
- Baseline PSA

Disease characteristics at study entry - NSCLC

Disease extent (metastatic, Loco Regional Recurrence, Primary, locally advanced) will be summarized.

Prior anticancer therapies

Prior anti-cancer treatments are collected by regimen in the eCRF. The following variables will be summarized:

- Prior chemotherapy (by category: 0, 1, 2, 3 or more regimens): Number (%) of patients who received Taxane chemotherapy will be summarized for mCRPC cohorts
- Number of prior regimens (by category: 1, 2, 3, >3)
- Prior radiation therapy: number (%) of patients with any prior radiotherapy related to mCRPC or NSCLC by intent
- Prior surgery: number (%) of patients with any prior surgery related to mCRPC or NSCLC by type of procedure (Preferred Term)

In addition, for mCRPC cohorts, prior hormonal therapy will be summarized by category (1, 2, 3 or more regimens). Number (%) of patients who received enzalutamide only, abiraterone only and enzalutamide + abiraterone will be summarized.

For NSLCL cohort, number (%) of patients who received anti-PD1/PDL-1 containing regimen will be summarized by category (1, 2 or more regimens).

2.1.2 Prior or concomitant medications (other than anticancer therapies)

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD), using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior to first study treatment administration. Prior medications can be discontinued before first dosing or can be ongoing during treatment phase

- Concomitant medications are any treatments received by the patient concomitantly to the study treatment from first administration to the last administration + 30 days. A given medication can be classified both as a prior medication and as a concomitant medication
- Post-treatment medications are those the patient took in the period running from the day after the last study treatment administration + 30 days up to the end of the study

Infusion associated reaction (IAR) medications

As defined in Section 8.2 of the study protocol, patients were to routinely receive premedications prior to isatuximab infusion to reduce the risk and severity of hypersensitivity reactions commonly associated with monoclonal antibodies. Premedications are defined in the protocol as non-investigational medicinal product(s). Premedications are reported on a specific eCRF page.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint for the Phase 2 part of the study is RR.

For patients with NSCLC, the RR is defined as the proportion of patients achieving complete response (CR) or partial response (PR) as best overall response (BOR), assessed by the investigator per RECIST 1.1 criteria, relative to the total number of patients in the analysis population. The confirmation of complete or partial response is required to determine BOR. BOR will be derived per RECIST 1.1 criteria using disease assessments performed from the first dose of treatment through the study excluding any assessments performed after the cutoff date or following the initiation of a further anticancer treatment. Clinical deterioration will not be considered as progression in the primary analysis of RR.

For patients with mCRPC, response will be defined by radiographic objective response (achieving CR or PR as BOR for soft tissue) assessed and confirmed by the Investigators and/or a PSA decline of ≥50% from baseline that is subsequently confirmed per PCWG3 criteria (protocol Appendix A). The PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later. BOR for soft tissue will be Non-CR/Non-PD for patients with no baseline target and non-target lesions identified at baseline and no new lesions reported in post-baseline tumor assessments.

2.1.3.2 Secondary efficacy endpoint(s)

The secondary efficacy endpoints are:

- Tumor burden change: Tumor burden change is defined as the best percent-change from baseline in a sum of the diameters (longest for non-nodal lesion, short axis for nodal lesions) for all target lesions

Area under the curve (AUC) of percent-change from baseline in tumor burden is defined as the area under the percent-change from baseline versus time curve calculated using the trapezoidal method from the date of the first post-baseline assessment to the date of the last assessment

The time-adjusted AUC of percent-change from baseline in tumor burden is defined as AUC of percent-change from baseline in tumor burden divided by the duration of the assessment

- Duration of response: Duration of response is defined as the time from the date of first response (PR or CR in radiographic objective response, or PSA decline ≥50% for patients with mCRPC) that is subsequently confirmed to the date of first disease progression or death, whichever occurs first. Disease progression includes radiographic disease progression or unequivocal clinical progression. The RECIST 1.1 criteria will be followed for assessment of radiographic disease progression in patients with NSCLC and the PCWG3 criteria will be followed in patients with mCRPC. For patients with mCRPC, radiographic progression includes progression by PCWG3 modified RECIST 1.1 for soft tissue and/or PCWG3 defined progression by bone scan. In the absence of disease progression or death before the analysis cut-off date or the date of initiation of a further anticancer treatment, the DOR will be censored at the date of the last valid response assessment not showing disease progression performed prior to initiation of a further anticancer treatment and the analysis cut-off date, whichever is earlier. DOR will not be calculated for patients who do not achieve a response
- Progression-free survival: For mCRPC patients, PFS is defined as the time from first study treatment administration to the date of first documented disease progression or the date of death from any cause, whichever occurs first. Disease progression includes radiographic disease progression (per PCWG3 criteria) or unequivocal clinical progression. For NSCLC patients, PFS is defined as the time from first study treatment administration to the date of first documented radiographic progression (per RECIST 1.1) or the date of death from any cause, whichever occurs first

  For patients who did not experience documented disease/radiographic progression or death before the analysis cut-off date or the date of initiation of new anticancer treatment, PFS will be censored at the date of the last valid disease/radiographic assessment not showing disease progression performed prior to initiation of a further anticancer treatment or the analysis cut-off date, whichever comes first. In addition, patient without PFS event (death or documented disease/radiographic progression) and without any valid post-baseline disease assessments will be censored at the day of first treatment (Day 1)
- Disease control rate (DCR): DCR is defined as the proportion of patients with confirmed complete response (CR) or partial response (PR) or stable disease (SD), as assessed by Investigator (per PCWG3 criteria for mCRPC patients and per RECIST 1.1 criteria for NSCLC patients) relative to the total number of patients in the analysis population

2.1.3.3 Exploratory efficacy endpoint(s)

For patients with mCRPC and patients with NSCLC, the following endpoints will be summarized:

- Overall survival (OS): defined as the time from first study treatment administration to death for any cause. Patients without death prior to the analysis cut-off date will be censored at the last date the patient was known to be alive or the cut-off date, whichever comes first
- Time to response: defined as the time from first study treatment administration to the first response (PR or CR in radiographic objective response, or PSA decline ≥50% for patients with mCRPC) that is subsequently confirmed (RECIST 1.1 for patient with NSCLC and PCWG3 criteria for patients with mCRPC)
- PFS by modified response evaluation criteria in solid tumors for immune based therapies (iRECIST) (3): is defined as the time from first study treatment administration to the date of first documented disease progression that is subsequently confirmed or the date of death from any cause, whichever occurs first. The same censoring rule as PFS will be used

In addition, the following endpoints will be summarized for patients with mCRPC:

- Disease control rate (DCR) ≥6 months: DCR ≥6 months includes patients with BOR of CR or PR of any duration or SD of ≥6 months duration. Duration of SD is defined as the time from the date of first treatment to the date of first disease progression or death due to any cause, whichever occurs first. Disease progression includes radiographic disease progression (per PCWG3 criteria) or unequivocal clinical progression. In the absence of disease progression or death before the analysis cut-off date or the date of initiation of a further anticancer treatment, the duration of SD will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anticancer treatment and the analysis cut-off date, whichever is earlier

  DCR ≥6 months rate is defined as the proportion of patients with DCR ≥6 months relative to the total number of patients in the analysis population

  Similarly, DCR ≥6 months rate requiring PD confirmation will also be summarized
- Radiographic PFS (rPFS): For mCRPC patients, rPFS is defined as the time from first study treatment administration to the date of first documented radiographic progression or the date of death from any cause, whichever occurs first. The same censoring rule as PFS will be used
- rPFS by iRECIST: For mCRPC patients, rPFS is defined as the time from first study treatment administration to the date of first documented radiographic progression that is subsequently confirmed or the date of death from any cause, whichever occurs first. The same censoring rule as PFS will be used
- PSA response rate: defined as a PSA decline of ≥50% from baseline that is subsequently confirmed
- Radiographic RR: defined as radiographic objective response assessed and confirmed by investigator

- Duration of PSA response: defined as the time from the date of the PSA first decline of ≥50% from baseline that is subsequently confirmed to the date of first confirmed PSA progression or death, whichever occurs first. PSA progression for patients who have achieved a ≥50% decrease from baseline is defined as at least a 25% increase and an absolute increase of ≥2 ng/mL above the nadir (the lowest PSA value on study). The same censoring rules as for DOR will be used
- Duration of radiographic response: defined as the time from the date of the first radiographic response (PR or CR) that is subsequently confirmed to the date of first radiographic progression or death, whichever occurs first. The same censoring rules as for DOR will be used
- Time to PSA response: defined as the time from first study treatment administration to the first PSA response that is subsequently confirmed
- Time to radiographic response: defined as the time from first study treatment administration to the first radiograph response that is subsequently confirmed
- Time to PSA progression: defined as the time from first study treatment administration to the date of first confirmed PSA progression. For patients who have achieved a ≥50% decrease from baseline, PSA progression is defined as at least a 25% increase and an absolute increase of ≥2 ng/mL above the nadir (the lowest PSA value on study). For patients without a PSA decrease of this magnitude or no decrease at all, PSA progression is defined as at least a 25% increase and an absolute increase of ≥2 ng/mL above the baseline. Death from prostate cancer or any other cause without prior evidence of PSA progression will not count as an event. If no event exists, then time to PSA progression will be censored at the last scheduled PSA assessment on study or date of death, whichever occurs first

For patients with NSCLC, the following endpoint will also be summarized:

- ORR by iRECIST (NSCLC patients): defined as the proportion of patients achieving complete response (CR) or partial response (PR) as best overall response (BOR) as assessed by the investigator per iRECIST criteria relative to the total number of patients in the analysis population

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, weight, electrocardiogram (ECG) and Eastern Cooperative Oncology Group (ECOG) performance status.

Observation period

The observation period starts from the time when the patient gives informed consent and is divided into 3 periods:

- **The pre-treatment period** is defined as the time informed consent is signed until the first dose of study treatments administration

- The **treatment-emergent adverse event (TEAE) period** is defined as the time from the first dose of study treatments up to 30 days after last dose of study treatments
- The **post-treatment** period is defined as the time starting from 31 days after the last dose of study treatments to the end of the study (as defined in the protocol)

2.1.4.1 Dose limiting toxicities (DLTs)

For the phase 1 part dose limiting toxicities will be listed by patient using the DLT evaluable population.

2.1.4.2 Adverse events variables

AEs (including serious adverse events [SAEs] and AEs of special interest [AESIs]) will be collected from the time of signed informed consent until the end of study.

Adverse event observation period

- **Pre-treatment AEs** are defined as any adverse event reported during the pre-treatment period
- **TEAEs** are adverse events that developed or worsened or became serious during the TEAE period
- **Post-treatment AEs** are adverse events that developed or worsened or became serious during the post-treatment period

All AEs (including SAEs and AESIs) will be graded according to NCI-CTCAE v4.03 and coded to a lower-level term, preferred term (PT), high-level term, high-level group term and associated primary system organ class (SOC) using the version of MedDRA currently in effect at Sanofi at the time of database lock.

Adverse events of special interest

Specific analyses will be performed for the following AEs:

- **DLTs**
- **Grade ≥2 IARs**. An IAR occurs typically within 24 hours from the start of the infusion
- **Grade ≥3 immune-related TEAEs**
- **Immune-related AEs of any grade in a patient previously treated with a PI3K inhibitor (only applicable for patients who receive REGN2810)**
- **Pregnancy** of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/non-investigational medicinal product (NIMP)
- **Symptomatic overdose** (serious or non-serious) with IMP/NIMP

2.1.4.3 Infusion associated reactions

IARs typically occur within 24 hours from the start of each isatuximab/REGN2810 infusion.

Whenever possible, a diagnosis of the IAR (eg, Cytokine release syndrome, infusion related reaction, anaphylactic reaction, or any other teams chosen by the investigator) will be reported by the investigator in a specific AE page. In addition, symptoms of the IARs will be reported on a separate eCRF form.

IARs will be analyzed based on the investigator reported term collected in the specific AE pages.

2.1.4.4 Deaths

The deaths will be summarized as follows:

- Deaths in TEAE period: includes all deaths occurring from the first IMP up to the end of treatment + 30 days
- Deaths in post-treatment period: includes all deaths occurring after the end of TEAE period up to study closure

2.1.4.5 Laboratory safety variables

Clinical laboratory data consists of blood and urine analysis including hematology, biochemistry and urinalysis. Clinical laboratory values will be converted into standard international units that will be used in all listings and tables.

Parameters measured on the day of the first study treatment infusion will be considered as part of the baseline measurements.

For laboratory safety variables, the treatment period is defined as the time from the first dose of study treatment (irrespective of treatment) administration to the last dose of study treatments + 30 days.

Blood and urine samples for clinical laboratories parameters will be taken as defined in the study flow charts and as clinically indicated. The laboratory parameters will be classified as follows:

- Hematology
  - **Hemoglobin and coagulation**: hemoglobin, hematocrit, red blood cell (RBC) platelet counts, prothrombin time or international normalized ratio (INR) and activated partial thromboplastin time (PTT)
  - **White blood cells (WBCs)**: WBC count, leukocytes, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Biochemistry
  - **Metabolism**: fasting glucose, total protein
  - **Electrolytes**: sodium, potassium, chloride, calcium, albumin, magnesium, phosphate, bicarbonate/carbon dioxide

- **Renal function**: uric acid, serum creatinine, estimated creatinine clearance by modified diet in renal disease (MDRD) formula, urea or blood urea nitrogen (BUN)
- **Liver parameters**: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total and direct bilirubin, lactate dehydrogenase (LDH)
- **Hormonal:** thyroid stimulating hormone (TSH) and free T4

- Urinalysis
  - Quantitative or semi-quantitative urinalysis: RBC, protein, glucose, pH, ketone, bilirubin, leukocytes, nitrates and specific gravity

2.1.4.6 Vital signs variables

Vital signs include: heart rate, systolic and diastolic blood pressure, respiratory rate, weight and temperature.

For vital signs, each assessment performed at cycle 1 Day 1, Day 8 and Day 15 prior to study treatment administration unless specified otherwise and at cycle N, Day 1.

Thus, parameters measured on the day of the first study treatment infusion will be considered as part of the baseline measurements.

For vital signs, the treatment period will start at first study treatment infusion + 1 day.

For a given parameter, a patient (respectively a cycle) will be considered as evaluable if at least one measure of this parameter is available during the on-treatment period.

2.1.4.7 Electrocardiogram variables

12-lead ECG assessments will be described as normal or abnormal.

2.1.4.8 Immunogenicity variables

Anti-drug antibodies (ADA) against isatuximab and REGN2810 will be collected according to the pharmacokinetics/pharmacodynamics (PK/PD) flowcharts in Section 1.5 of the protocol.

ADA attributes

Pre-existing ADA is defined as ADA reactive with the biotherapeutic present in subjects before treatment (or before initiation of the clinical study).

Treatment boosted ADA is defined as pre-existing ADAs that were boosted to a higher level following administration of biotherapeutic (ie, any time after the initial drug administration) the ADA titer is significantly higher than the baseline titer. A low serial dilution schema (2-fold or 3 fold) should be applied during titration. A difference in titer values of two titer steps between treatment or follow-up sample and its baseline sample is considered significant. For examples, at least a 4-fold increase in titers for 2- fold serial dilution schema (or 9–fold increase in titers for 3- fold serial dilution schema). If no titer could be determined for a positive sample, the titer will be reported as the minimal required dilution of the assay.

Treatment-induced ADA is defined as ADAs developed de novo (seroconversion) following administration of the biotherapeutic (i.e., formation of ADAs any time after the initial drug administration in a subject without pre-existing ADAs). If the baseline ADA sample is missing or non-reportable and at least one reportable ADA sample is available during the treatment (including follow-up period) the baseline sample will be considered as "negative" for data analysis. This is considered being a conservative approach for ADA assessment.

Subject status

Among evaluable population for immunogenicity (described in Section 2.3.5), following patient status will be defined:

- **ADA-positive** subject: A subject with at least one treatment induced or treatment boosted ADA-positive sample at any time during the treatment or follow-up observation period
- **ADA-negative** subject: Subject without any treatment induced or treatment boosted ADA-positive sample during the treatment or follow-up observation period
- **ADA-inconclusive** subject: A subject who cannot irrefutably be classified as ADA negative (eg, all post baseline samples inconclusive)

Overview of the ADA response

Two main categories can be reported for the epidemiology of an ADA immune response: ADA prevalence and ADA incidence:

- **ADA prevalence** defines the proportion of all subjects tested positive for ADAs (including preexisting antibodies, treatment boosted ADAs and treatment induced ADAs) at any point in time
- In contrast the term **ADA incidence** only defines the proportion of subjects found to either have seroconverted (treatment induced ADAs) or boosted their pre-existing ADA response during the study. Only evaluable subjects (described in Section 2.3.5) are considered for computing ADA incidence

Kinetics of the immune response

- **Onset of ADA:** refers to the time period between the initial drug administration and the first instance of treatment induced ADAs. The use of real-elapsed days should be used for the calculations. The "median time to ADA development" and the quartiles Q1 and Q3 should be reported
- **Duration of ADA:** ADA duration will be calculated as the date of last treatment induced ADA sample minus date of first treatment induced or treatment boosted ADA sample +1; ADA duration will be calculated only for patients with at least two ADA positive samples. Median duration of an induced ADA response and the quartiles Q1 and Q3 should be reported
- **Transient ADA response** is defined by:
  - Treatment induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point), OR

- Treatment induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the patient's last sampling time point is ADA negative

- **Persistent ADA response** is defined by:
  - Treatment induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples are separated by at least 16 weeks (irrespective of any negative samples in between)
- **Indeterminate ADA** is defined by:
  - Treatment induced ADA detected only at the last sampling time point, OR
  - The last two samples being ADA-positive and separated by a period of less than 16 weeks

Treatment-boosted ADAs are excluded from the analysis of ADA kinetics.

2.1.5 Pharmacokinetic variables

The PK sampling times for isatuximab and REGN2810 were provided in the PK/PD flowchart in Section 1.5 of the protocol.

The following PK parameters (listed in Table 3) will be calculated with PKDMS software (Pharsight) V3.0, using non-compartmental method from isatuximab and REGN2810 concentrations after the first administration on Cycle 1. The parameters will include, but may not be limited to the following:

Table 3 - List of pharmacokinetic parameters and definitions

Parameters	Analyte		Definition
	REGN2810	Isatuximab	
Ceoi	X	X	Concentration observed at the end of intravenous (IV) infusion
Cmax	X	X	Maximum concentration observed
tmax	X	X	Time to reach Cmax
Clast	X	X	Last concentration observed above the lower limit of quantification
tlast	X	X	Time of Clast
AUC0-21d	X		Area under the concentration versus time curve calculated using the trapezoidal method over the dosing interval (21 days)
AUC0-7d or AUC0-21d		X	Area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (7 days, and for cohorts C and D: 21 days)

C_{trough} are defined as sample collected just before treatment administration during repeated dosing.

In addition, populations PK approaches may be used for both compounds and PK estimates may be used to conduct exploratory exposure-response analyses for safety and efficacy and PK/PD analyses for relevant biomarkers. If done, the data generated will be reported in stand-alone report(s).

2.1.6 Biomarker endpoints

2.1.6.1 Immune Genetic Determinants

Germline genetic data of Fc gamma receptor (FCGR) genes will be analyzed on blood samples collected on Day 1 of Cycle 1:

- FCGR polymorphisms (FCGR3A): For each gene, the results will be of the form AA, Aa or aa with A and a-alleles, the major and minor allele, respectively

2.1.6.2 Immune phenotyping

Immune phenotyping in peripheral blood (baseline, D1 of Cycle 1, 2, 3, 5, 7, 9, end of treatment (EOT) and FUP60) will be assessed. Immune cell sub-populations will be determined by multiparametric flow cytometry based on the expression of different cell surface markers. Percentages of a given immune cell sub-populations and absolute counts as well as expression intensity of certain markers will be provided.

2.1.6.3 PD-L1 expression singleplex IHC

PD-L1 expression on tumor and immune cells will be assessed using tumor tissue (freshly collected tumor biopsy or archival tissue) biopsy at Screening/Baseline and (unless clinically unfeasible) at C2D1.

2.1.6.4 Cluster of differentiation 38 (CD38) expression singleplex IHC

CD38 expression on tumor and immune cells will be assessed using tumor tissue (freshly collected tumor biopsy or archival tissue) biopsy at Screening/Baseline and (unless clinically unfeasible) at C2D1.

2.1.6.5 Immune cell subpopulation tumor infiltration and markers co-expression multiplex immunofluorescence

Immune cell subpopulation tumor infiltration and markers co-expression on different cell sub-populations will be assessed on tumor tissue (freshly collected tumor biopsy or archival tissue) biopsy at Screening/Baseline and (unless clinically unfeasible) at C2D1. Cell sub-populations will be determined by multiplex Immunofluorescence based on the expression of 12 different cell markers. The results will be provided per region of interest (ROI) and the number of cell sub-populations will be provided for 3 regions (total, within tumor, outside tumor).

Per cell sub-population, an average of the results provided per ROI will be calculated for the totality of tumor tissue.

2.1.7 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapies after discontinuation of study treatment will be collected on a specific eCRF page. The following information will be collected: drug/medication (brand or generic name), start date and end date (if available)/ongoing (otherwise).

2.2 DISPOSITION OF PATIENTS

Patient disposition will be summarized by cohort based on the analysis population defined in Section 2.3.

Screened patients are defined as any patients who signed the study informed consent.

Enrolled patients are screened patients who are planned to receive the study treatment, ie, for whom the investigator ticked "Yes" to the question "Will the patient continue into the study?" at the end of the screening period.

Randomized patients include all patients in cohort A-1 stage 2 and cohort A-2 who signed the study informed consent and were randomized regardless of whether the patient was treated or not.

For patient study status, the total number of patients for each of the following categories will be presented in the clinical study report using a flow-chart diagram or a summary table:

- Screened patients
- Enrolled/randomized patients
- Enrolled/randomized and not treated patients
- Enrolled/randomized and treated patients
- Patients still on treatment
- Patients completed treatment
- Patients who discontinued the study treatments period and reasons for permanent discontinuation

The number and percentage of patients in analysis population (defined in Section 2.3) will be provided in a summary table.

A summary of the reasons for definitive and premature treatment discontinuation for either treatment will be provided. Definitive treatment discontinuation is defined as the discontinuation of all the study treatments. Premature treatment discontinuation (only for cohorts with the combination therapy) is defined as the discontinuation of one of the study treatments but the other one continued. Listing of the reasons for treatment discontinuation will be provided.

The number (%) of patients treated by country and center will be summarized using the all-treated population (defined in Section 2.3).

All critical or major deviations potentially impacting efficacy and safety analyses will be summarized by cohort separately. Critical or major protocol deviations will be listed.

2.2.1 Randomization and drug dispensing irregularities

For patients with mCRPC, if an isatuximab monotherapy cohort is initiated, patients with mCRPC will be randomly assigned in a 1:1 randomization ratio to enter Cohort A-1, isatuximab and REGN2810 combination (Phase 2 Stage 2) or Cohort A-2, isatuximab monotherapy (Phase 2 Stage 1).

All randomization and drug-dispensing irregularities will be documented in the clinical study report. The irregularities will be categorized and summarized among randomized patients (number and percentages).

2.3 ANALYSIS POPULATIONS

2.3.1 All-treated population

For both Phase 1 and Phase 2 parts of the study, the all-treated population will include all patients who signed the study informed consent and received at least 1 dose (even incomplete) of the study treatments, either isatuximab or REGN2810.

This population is the primary population for the analyses of efficacy and safety parameters except for DLT evaluation. All analyses using this population will be based on the dose level actually received in the first cycle.

2.3.2 DLT-evaluable population

The DLT evaluable population is defined as patients in the Phase 1 part receiving the planned doses of isatuximab and REGN2810 during Cycle 1, and who completed the DLT observation period after the first IMP administration as per Section 9.1.1 from protocol, unless they discontinue the study treatment(s) due to DLT. The dose recommended for Phase 2 will be determined on the DLT evaluable population.

2.3.3 Pharmacokinetic population

The PK population will be defined independently for isatuximab and REGN2810, and include patients from the all treated population with at least one reportable concentration after the study drug administration (whatever the cycle and even if dosing is incomplete).

2.3.4 Pharmacodynamic population

The pharmacodynamic population will include patients from the all-treated population with at least 1 pharmacodynamic marker result after the first dose of study treatment.

2.3.5 Anti-drug antibody (ADA) evaluable population

The ADA evaluable population will be defined independently for isatuximab and REGN2810, and include subjects with at least one sample, taken post-baseline after drug administration during the

treatment or follow-up observation period, that is appropriate for ADA testing with a reportable result (positive, negative or inconclusive).

2.3.6 Cross-over population

The cross-over population is defined as patients in Cohort A-2 who progressed on isatuximab monotherapy and received isatuximab in combination with REGN2810.

2.3.7 Response evaluable population

The response evaluable population will include all patients in the all-treated population who fulfilled all inclusion and exclusion criteria with an evaluable baseline assessment and at least one evaluable post-baseline disease assessment during the treatment period.

2.4 STATISTICAL METHODS

Continuous data will be summarized using number of available data, mean, standard deviation, median, minimum and maximum for each dose level (if applicable). Categorical and ordinal data will be summarized using number and percentage of patients.

Data listings will be provided separately by cohort and sorted by patient number, unless otherwise specified.

2.4.1 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized on the all-treated population. Parameters described in Section 2.1.1 will be summarized using descriptive statistics.

The medical and surgical history will be summarized according to the SOC and PT (SOC will be sorted according to the internationally agreed order and PT by overall decreasing frequency).

Disease characteristics at diagnosis and at study entry will be described.

2.4.2 Prior or concomitant medications (other than anticancer therapies)

The prior, concomitant and post medications will be presented for the all-treated population. The anti-cancer therapy will be presented separately.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomic therapeutic category (ATC) class and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and the patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore the patients may be counted several times for the same medication.

The tables for medications (prior, concomitant and post-treatment) will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence. In case of equal frequency regarding ATCs, alphabetical order will be used.

IAR medications

Number (%) of patients with IAR medications as defined in Section 2.1.2 will be provided.

2.4.3 Anticancer therapies

Prior anti-cancer treatments will be summarized for the all-treated population. Number (%) of patients with the anti-cancer treatments described in Section 2.1.1 will be summarized. In addition, prior anti-cancer treatments after disease became mCRPC for prostate patients or after disease became advanced for NSCLC patients will be summarized.

2.4.4 Extent of investigational medicinal product exposure and compliance

The extent of study treatment exposure will be assessed and summarized on the all-treated population.

2.4.4.1 Extent of investigational medicinal product exposure

The overall extent of exposure will be assessed as:

- Overall number of cycles started
- Duration of overall exposure (weeks): defined as (last day of last cycle – first day of first cycle)/7. The first day of first cycle is defined as the date of the first dose of study treatments. The last day of last cycle is defined as the later date among the following:
  - Date of the last dose of isatuximab + 7 days if the last cycle is a QW cycle or date of the last dose of isatuximab + 21 days if the last cycle is a Q3W
  - Date of the last dose of REGN2810 + 21 days

Total number of cycles started, number of cycles started by patient as a continuous variable and by category (ie, number [%] of patients receiving at least 1 cycle, at least 2 cycles, etc.), duration of overall exposure will be summarized using descriptive statistics.

To describe overall dose modification, the cycle delay will be summarized. A cycle is considered as delayed if the start date of cycle – 21 – the start date of the previous cycle is >3 days. They cycle start date is defined as the earlier date of isatuximab or REGN2810 administration within a cycle. Cycle delay is not defined for the first cycle.

Cycle delay will be summarized at both the patient and cycle levels as follows:

- Patient level:
  - Number of patients treated
  - Number (%) of treated patients with at least 1 cycle delayed
    - Number (%) of treated patients with a cycle delayed between 4 and 7 days
    - Number (%) of treated patients with a cycle delayed between 8 and 14 days
    - Number (%) of treated patients with a cycle delayed more than 14 days

- Cycle level:
  - Number of cycles started
  - Number (%) of cycles delayed
    - Number (%) of cycles delayed between 4 and 7 days
    - Number (%) of cycles delayed between 8 and 14 days
    - Number (%) of cycles delayed more than 14 days

2.4.4.2 Isatuximab exposure

The isatuximab exposure will be summarized as follows:

- Total number of cycles started
- Number of cycles started by patient as a continuous variable and by category
- Duration of isatuximab exposure (weeks) is defined as
  - (Date of the last dose of isatuximab + 7 days – date of the first dose of isatuximab)/7 if the last cycle is a QW cycle
  - (Date of the last dose of isatuximab + 21 days – date of the first dose of isatuximab)/7 if the last cycle is a Q3W cycle
- Actual dose (mg/kg): is defined as the actual dose (mg) administered divided by the body weight at the time
- Cumulative dose (mg/kg): the cumulative dose is the sum of all actual doses (mg/kg) of isatuximab given from the first to the last administration
- Actual dose intensity (ADI, mg/kg/week): is defined as the cumulative dose (mg/kg) divided by the duration of isatuximab exposure (weeks)
- Relative dose intensity (RDI, %): $100 \times \frac{\text{ADI (mg/kg/week)}}{\text{Planned Dose Intensity (mg/kg/week)}}$.

  Planned dose intensity (mg/kg/week) corresponds to the planned dose (mg/kg) multiplied by the theoretical total number of doses during the started cycles (3 for QW cycle and 1 for Q3W cycle) and divided by the theoretical cycle duration (weeks), ie, 3 weeks per cycle started.

The total number of cycles started, number of cycles started by patients as a continuous variable and by category (ie., number [%] of patients receiving at least 1 cycle, at least 2 cycles, etc.), duration of isatuximab exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following variables will be derived to describe dose delay and modification:

- Dose delay within Cycle 1: a dose is deemed as delayed within Cycle 1 if the actual start date of the infusion is ≥2 days beyond the theoretical day of treatment for weekly dose. Dose delay does not apply to the first infusion of Cycle 1

- Infusion interruption: an infusion is considered to be interrupted (as collected on eCRF) if the isatuximab administration is stopped during an infusion before it is completed regardless of whether it is further restarted or not
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are dose(s) administered afterwards

Dose delay and modification will be summarized at the patient and infusion levels as follows:

- Patient level:
  - Number (%) of patients with at least 1 dose delay within cycle
  - Number (%) of patients with at least 1 dose omission
  - Number (%) of patients with at least 1 infusion interrupted
    - Number (%) of patients with at least 1 infusion interrupted and re-started
    - Number (%) of patients with at least 1 infusion interrupted and not re-started
- Infusion level:
  - Number of isatuximab infusions
  - Number (%) of infusions interrupted
    - Number (%) of infusions interrupted and re-started
    - Number (%) of infusions interrupted and not re-started
  - Number (%) of infusions interrupted more than once
  - Number (%) of infusions interrupted at 1st infusion, 2nd infusion, subsequent infusions
  - Time from infusion start to first interruption in minutes summarized as a continuous variable and by category (<5 minutes, 5-10 minutes, etc.)

2.4.4.3 REGN2810 exposure

The REGN2810 exposure will be summarized as follows:

- Total number of cycles started
- Number of cycles started by patient as a continuous variable and by category
- Duration of REGN2810 exposure (weeks) is defined as (Date of the last dose of REGN2810 + 21 days – Date of the first dose of REGN2810)/7
- Actual dose (mg): is defined as actual dose administered
- Cumulative dose (mg): the cumulative dose is the sum of all actual REGN2810 doses
- ADI (mg/week): is defined the cumulative dose (mg) divided by the duration of REGN2810 exposure (weeks)
- RDI (%): $100 \times \frac{\text{ADI (mg/week)}}{\text{Planned Dose Intensity (mg/week)}}$, where the planned dose intensity (mg/week) is 116.7 mg/week for Q3W schedule

The total number of cycles started, number of cycles started by patients as a continuous variable and by category (ie, number [%] of patients receiving at least 1 cycle, at least 2 cycles, etc), duration of REGN2810 exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following variables will be derived to describe dose delay and modification:

- Infusion interruption: An infusion will be considered to be interrupted (as collected on eCRF) if the REGN2810 administration is stopped during an infusion before it is completed regardless of whether it is further restarted or not
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are positive dose(s) afterwards

Dose delay and modification will be summarized at the patient and infusion levels as follows:

- Patient level:
  - Number (%) of patients with at least 1 dose omission
  - Number (%) of patients with at least 1 infusion interrupted
    - Number (%) of patients with at least 1 infusion interrupted and re-started
    - Number (%) of patients with at least 1 infusion interrupted and not re-started
- Infusion level:
  - Number of REGN2810 infusions
  - Number (%) of infusions interrupted
    - Number (%) of infusions interrupted and re-started
    - Number (%) of infusions interrupted and not re-started
  - Number (%) of infusions interrupted more than once
  - Number (%) of infusions interrupted at 1st infusion, 2nd infusion, subsequent infusions
  - Time from infusion start to first interruption in minutes summarized as a continuous variable and by category (<5 minutes, 5-10 minutes, etc.)

2.4.5 Analyses of efficacy endpoints

All efficacy analysis will be performed using the all-treated population. In addition, efficacy analysis will be performed using the response evaluable population.

For each cohort, the analysis cut-off date for the primary analysis of RR will be 6 months after the last patient's first treatment in the cohort. The analysis cut-off date for secondary efficacy endpoints including DoR and PFS will be 12 months after the last patient's first treatment in the cohort. The primary analysis of RR will be updated.

2.4.5.1 Analysis of primary efficacy endpoint(s)

The RR will be summarized using descriptive statistics. A 90% 2-sided confidence interval will be computed using Clopper-Pearson method. BOR will be summarized descriptively. For mCRPC cohorts, PSA response will also be summarized using descriptive statistics.

2.4.5.2 Analyses of secondary efficacy endpoints

The secondary efficacy endpoints are:

- Tumor burden change: the best percent-change from baseline in tumor burden will be summarized and presented graphically for patients with measurable disease at baseline. In addition, a summary of the AUC and the time-adjusted AUC of percent-change from baseline in tumor burden will also be provided as an exploratory analysis
- DoR: Kaplan-Meier estimates such as median and Kaplan-Meier curves will be provided for patients who achieved a response (PR or CR, or PSA response for mCRPC patients)
- PFS: the PFS will be analyzed using the Kaplan-Meier method. The Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and the 95% confidence intervals of median will also be computed. The Kaplan-Meier curves will be plotted. In addition, PFS at 6 months will also be provided

DCR ≥6 months, PSA response rate, radiographic RR for mCRPC patients and ORR by iRECIST for NSCLC patients will be summarized with descriptive statistics. OS, time to response, and PFS by iRECIST will be analyzed using the Kaplan-Meier method. In addition, for mCRPC patients, rPFS, rPFS by iRECIST, duration of PSA response, duration of radiographic response, time to PSA response, time to radiographic response, and time to PSA progression will be also be analyzed using the Kaplan-Meier method.

2.4.5.3 Multiplicity issues

Not applicable.

2.4.6 Analyses of safety data

The all-treated population will be used for all safety analyses except for the DLT analysis in Phase 1, which will be performed based on the DLT-evaluable population.

2.4.6.1 Analyses of DLTs (Phase 1 only)

The DLTs will be listed by patient using the DLT-evaluable population in Phase 1.

2.4.6.2 Analyses of adverse events

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pre-treatment and post-treatment adverse events will be described separately.

If an AE date of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pretreatment, treatment-emergent, or post-treatment. The algorithm for imputing date of onset will be conservative and will classify an AE as treatment emergent unless there is definitive information to determine it is pretreatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Regarding treatment discontinuation, following definitions will be used:

- **Premature** treatment discontinuation is defined when 1 of the IMPs is permanently discontinued, subjects will continue receiving the other IMP until study treatment permanent discontinuation
- **Definitive** treatment discontinuation is defined as the discontinuation of all the study drugs

The severity grade will be taken into account in the summary. For patients with multiple occurrences of the same AE, the maximum (worst) severity grade by period of observation will be used. Summaries will be provided for all grades and for Grade ≥3 (including grade 5). Missing grades handling is provided in Section 2.5.3.

Sorting within tables should ensure the same presentation for the set of all AEs for each observation period (pre-treatment, treatment-emergent and post-treatment). For that purpose, tables of all TEAEs by SOC and PT will be sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs. This order will define the presentation order for all other tables unless otherwise specified.

Overall summary of TEAEs

An overall summary of TEAEs will be provided. The number (%) of patients who experience any of the following will be provided:

- TEAE
- TEAE of Grade ≥3
- TEAE of Grade 5
- Serious TEAE
- Treatment-related TEAEs (any grade)
- Treatment-related TEAEs of ≥Grade 3
- Serious treatment-related TEAEs
- TEAE leading to definitive study treatment discontinuation
- TEAE leading to premature discontinuation of isatuximab
- TEAE leading to premature discontinuation of REGN2810
- AESI
- AESI of Grade ≥3

Analysis of all TEAEs

The number (%) of patients experiencing TEAEs by primary SOC and PT will be summarized by grade (all grades and Grade ≥3). Similar tables will be presented for treatment-related TEAEs, serious TEAEs, and TEAEs leading to definitive/premature discontinuation.

TEAEs with an incidence ≥5% will be summarized by PT for all grades and Grade ≥3.

Listings of serious TEAEs, TEAEs leading to definitive or premature treatment discontinuation will be provided.

Infusion associated reactions (IARs)

IAR analysis will include all adverse events regardless of relationship to isatuximab, cemiplimab or NIMP. The IARs will be summarized as follow:

- Number (%) of patients experiencing IARs according to investigator reported AEs presented by primary SOC and PT will be summarized by grade,
- Description of the IAR diagnoses (using the diagnosis reported and excluding symptoms)
  - Number (%) of patients action taken
  - Number (%) of patients with only 1, ≥1, ≥2, ≥3, ≥4 and ≥5 episodes
  - Number (%) of patients with first occurrence of IAR at the first infusion and subsequent infusions
  - Number (%) of patients with IAR at the first and subsequent infusions
  - Number (%) of patients with at least two episodes of IRs at the same infusion
  - Day of onset from infusion
  - Duration (in days)
- Number of patients with symptoms of IRs (as reported by investigator) by SOC and PT

Analysis of adverse events of special interest

A listing of patients with at least one AESI described in Section 2.1.4.2 will be provided.

Analysis of pre-treatment and post-treatment adverse events

The following analysis will be provided by grade (all grades and Grade ≥3).

- All pre-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 pre-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All post-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 post-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

2.4.6.3 Deaths

The following summaries of deaths will be generated:

- Number (%) of patients who died by study period (on-treatment, post-treatment) and reasons for death (disease progression, AE, other)
- TEAEs with fatal outcome (on the AE eCRF page as reported by the Investigator), and TEAEs with fatal outcome during the post-treatment period summarized by SOC and PT

2.4.6.4 Analyses of laboratory variables

Each laboratory test result will be graded by CTCAE criteria (version 4.03), when applicable. For hematological parameters and for some biochemistry parameters, Sanofi sponsor generic normal ranges will be used for the grading of laboratory abnormalities (see list of parameters in Table 6 and Table 7). For other biochemistry parameters (eg, for hepatic parameters), grading will be derived using the local laboratory normal ranges.

The number (%) of patients with abnormal laboratory tests at baseline and during the on-treatment period will be presented by all grades and each grade. For patients with multiple occurrences of the same laboratory variable during the on-treatment period, the maximum grade (worst) per patient will be used.

The denominator used for percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests and with Grade 3-4 abnormal laboratory tests.

2.4.6.5 Analyses of vital sign variables

The incidence of vital signs potentially clinically significant abnormality (PCSA) (Table 4) any time during the on-treatment period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

Table 4 - Potentially clinically significant abnormalities criteria for vital signs

Parameter	PCSA
HR	≤50 bpm and decrease from baseline ≥20 bpm
	≥120 bpm and increase from baseline≥20 bpm
SBP	≤95 mmHg and decrease from baseline ≥20mmHg
	≥160 mmHg and increase from baseline ≥20 mmHg
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg
	≥110 mmHg and increase from baseline ≥10 mmHg
Weight	≥5% increase from baseline
	≥5% decrease from baseline

Temperature and respiratory rate will be summarized at baseline and end of treatment. A listing of patients with at least one PCSA will be provided.

2.4.6.6 Analyses of electrocardiogram variables

A listing of patients with ECG results will be provided.

2.4.6.7 Analysis of Immunogenicity

Immunogenicity analysis will be done separately for isatuximab and REGN2810.

Number of evaluable patients, number (%) of pre-existing ADA and negative patients at baseline, number (%) of boosted and induced patients (either transient, persistent or indeterminate) will be reported, along with descriptive statistics of titer, by cohort and possibly overall. Prevalence and incidence will also be presented.

In addition, for positive ADA patients, time to onset, duration of ADA response, and the characterization of the immune response (transient, persistent, indeterminate) will be provided.

An individual data listing with ADA samples status (positive, negative or inconclusive), the titer if applicable, date of first/last dose, duration of exposure, study period, cycle/day, time point and date/time of sampling along with C_{trough} value of the drug will be provided for all patients.

The impact on safety and efficacy endpoints may be further explored by graphical methods or descriptively, depending on the ADA prevalence.

2.4.7 Analyses of pharmacokinetic variables

PK analysis will be done separately for isatuximab and REGN2810.

2.4.7.1 PK parameters

2.4.7.1.1 Cycle 1

Following the first administration, individual concentrations and PK parameters of drug will be listed and summarized by descriptive statistics (such as the number of observations, arithmetic and geometric mean, median, SD, SEM, CV%, minimum, and maximum) by cohort and possibly overall.

Individual and mean concentration profiles over time will be plotted by cohort and possibly overall under the responsibility of Sanofi, Pharmacokinetic, Dynamic and Metabolism (PKDM), Translational Medicine and Early Development (TMED) department.

2.4.7.1.2 Overall treatment: C_{trough} and C_{eoi}

C_{trough} defined as a sample collected before dosing, and in a time window of 12 to 16 days after the previous infusion for the Q2W administration, or in a time window of 6 to 8 days after the previous infusion for the QW administration will be included in the descriptive analysis irrespectively of interruption of infusion. However C_{trough} drawn outside collection of time window described in the protocol PKPD flowchart or collected after dose deviation higher than ±50% from intended dose will be excluded from the analyses.

C_{eoi} collected after significant infusion interruption, drawn outside collection of time window described in the protocol PKPD flowchart or collected after dose deviation higher than ±50% from intended dose will be excluded from the analyses.

Individual C_{trough} and C_{eoi} will be listed and summarized with same descriptive statistics as above by cohort and possibly overall.

Mean (±SE) of C_{trough} will be plotted over treatment phase by cohort and possibly overall for isatuximab and for REGN2810.

Individual C_{trough} ratio and C_{eoi} ratio (described in Table 5) will be listed and summarized by descriptive statistics by cohort and possibly overall as described above.

Table 5 - C_{trough} and C_{eoi} ratio

Analyte	C_{trough}	C_{eoi}
Isatuximab	C2D1 vs C1D8	C2D1 vs C1D1
	C4D1 vs C1D8	C4D1 vs C1D1
REGN2810	C4D1 vs C1D22	C4D1 vs C1D1

2.4.7.2 Immunogenicity impact on PK

Immunogenicity impact on PK analysis may be explored, depending on the ADA prevalence.

A descriptive statistics of C_{trough} as described above will be provided at each cycle in the subset of negative patients by cohort and possibly overall where positive or inconclusive patients will be observed.

A graphical representation of individual C_{trough} profile will be provided throughout the course of treatment by cohort and possibly overall where positive or inconclusive patients will be observed. Positive patients profile will be highlighted (eg, color or bold) and the concentration of isatuximab and REGN2810 at the same time as ADA positive result will be notified.

2.4.8 Analyses of biomarker variables

The biomarker variables will be summarized by clinical group (eg, DCR≥6 months for mCRPC patients vs. others) and overall. Graphics will be provided as appropriate. The biomarker variables include, but not limited to, the following variables:

- FCGR3A types: F/F, F/V, V/V and missing,
- CD38 expression
- PDL1 expression

Additional biomarker analysis may be conducted in an exploratory manner. Additional analysis, not specified in the protocol but related to the drug action and/or effect of isatuximab/REGN2810, may be conducted on remaining samples pending evolving literature.

2.4.9 Analyses of quality of life/health economics variables

Not applicable.

2.4.10 Further therapy after discontinuation of investigational medicinal product administration during the study

A listing of further therapy after discontinuation of investigational medicinal product administration during the study may be provided.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Creatinine clearance (eGRF) using the equation of MDRD formula:

$$GFR = 175 \text{ x } (Scr)^{-1.154} \text{ x } (Age)^{-0.203} \text{ x } (0.742 \text{ if Female}) \text{ x } (1.212 \text{ if African American})$$

with serum creatinine in mg/dL and age in year.

Corrected calcium formula:

Corrected Calcium (mmol/L) = Serum Calcium (in mmol/L) + 0.8 (4 - serum albumin [in g/dL])

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

2.5.3 Missing data

The analyses and summaries of continuous and categorical variables will be based on observed data only. Percentages will be calculated using as denominator the number of patients with non-missing observation in the considered population. When relevant, the number of patients with missing data is presented.

When incomplete or missing dates were found in the eCRF, attempts were made to retrieve the complete date, especially for dates within the month prior to first dose. However, if some dates remain incomplete, the following rules will be applied:

Handling of disease characteristics missing/partial dates

- If the day is missing, it will be estimated by 1
- If the month is missing, it will be estimated by 1 (only for medical history variables)
- If the year is missing, no estimation will be performed

Handling of medication missing/partial dates

No imputation of medication (other than anti-cancer therapies) start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

For prior anti-cancer therapies, following rules will be applied:

Missing/partial start date will be imputed as follows:

- If year and month exist, day is missing, impute as the first day of the month
- If only year exists, month and day are missing, impute as the first day of the year
- If year, month, and day are all missing, no imputation will be applied

Missing/partial end date will be imputed in a two-step approach as follows:

- Step 1: Use the following rule to impute end date:
  - If year and month exist, day is missing, impute as the first day of the month
  - If only year exists, month and day are missing, impute as the first day of the year
  - If year, month, and day are all missing, no imputation will be applied
- Step 2: If imputed end date is earlier than start date, set the imputed end date the same as start date

Imputation of incomplete date for post anti-cancer treatment start date

For post anti-cancer treatments, if the medication start date is missing, it will be imputed as follows:

- If the medication start day and month are missing and the medication start year is the same as treatment end year, the medication start date will be set equal to treatment end date + 1
- If the medication start day and month are missing and the medication start year is after the treatment end year, the medication start day and month will each be set to 01
- If the medication start day is missing and medication start year and month is the same as the treatment end year and month, the medication start day will be set equal to the treatment end day + 1
- If the medication start day is missing and medication start month is before the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01
- If the medication start day is missing and the medication start month is after the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01

- If the medication start day is missing and the medication start month is not missing and the medication start year is after the treatment end year, the medication start day will be set to 01
- If the medication start day, start month and start year is missing, the medication start date will be set equal to the treatment end date + 1

No imputation will be done for the missing/partial end date.

Handling of adverse events with missing or partial date of onset

Missing or partial adverse event onset dates (occurrence or becoming serious) will be imputed so that if the partial adverse event onset date information or visit number does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. In case of AEs worsening during the study, the emergence will also be based on the cycle of worsening. No imputation of adverse event end dates will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date of adverse event resolution.

Handling of death with missing or partial date of death

The imputation for missing or partial death date will proceed as follows:

- If the death day is missing and the death month and year are the same as the last month and year the patient was last known to be alive, the death day will be set equal to the last day the patient was known to be alive + 1
- If the death day is missing and the death month is after the month the patient was last known to be alive and the death year is the same as the year the patient was last known to be alive, the death day will be set to 01
- If the death day and month are missing and the death year is the same as the year the patient was last known to be alive, the death date will be set equal to the date the patient was last known to be alive + 1
- If the death day and month are missing and the death year is after the year the patient was last known to be alive, the death day and month will both be set to 01

If the date the patient was last known to be alive is partial or missing, no imputation for missing or partial death date will be performed. The last date the patient was known to be alive is the last of: date of last dose, date of last visit performed (when the patient is known to be alive according to subject vital status), date of last laboratory assessment, and date of last vital signs.

Handling of AEs with missing grade

If the grade is missing for one of the treatment emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, no imputation will be done and missing grades will be summarized in the “all grades” category.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to the regimen is missing, then the relationship to the regimen has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level. No imputation will be done for relationship to NMIP.

Handling of parameters expressed as inequality or approximation

For some parameters (such as laboratory parameters), if the value is expressed as "< xx", "≤xx, half of the numeric portion of the entry or limit of quantification will be used in calculations.

Handling of missing date/time in duration of infusion calculation

When both REGN2810 and isatuximab are given to a patient on the same visit:

- Missing REGN2810 end date/time will be imputed by isatuximab start date/time (if available)
- Missing isatuximab start date/time will be imputed by REGN2810 end date/time (if available)

Other types of missing date/time will not be imputed, and data will be excluded from the analysis of duration of infusion.

Handling of other missing dates

Incomplete date of cancer diagnosis:

- If the day of the cancer diagnosis is missing, the date will be imputed to the first day of the month
- If day and month of the cancer diagnosis are missing, no imputation will be done

Incomplete date of progression for the last prior regimen:

- If the day of the progression for the last prior regimen is missing, the date will be imputed to the end day of the month
- If day and month of the progression for the last prior regimen are missing, no imputation will be done

Incomplete date of prior surgery:

- If the day of the last prior surgery is missing, the date will be imputed to the end day of the month
- If day and month of the last prior surgery are missing, no imputation will be done

Incomplete date of prior radiotherapy:

- If the day of the last prior radiotherapy is missing, the date will be imputed to the end day of the month

If day and month of the last prior radiotherapy are missing, no imputation will be done.

2.5.4 Windows for time points

Laboratory data

A protocol planned laboratory test is considered to have occurred during a cycle if the date of sampling is after (>) the first day of the cycle, but prior to or equal (≤) to the first day of the next cycle. For unscheduled tests, a test is considered to have occurred during a cycle if the date of sampling is equal to or after (≥) the first day of the cycle, but prior (<) to the first day of the next cycle.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs and ECG will be used for computation of worst values and/or grades on treatment. Unscheduled visits prior to first administration will be also used for computation of baseline except if they are not collected on the day of first administration.

2.5.6 Pooling of centers for statistical analyses

Data from all sites will be pooled together for analyses.

2.5.7 Statistical technical issues

Not applicable

3 INTERIM ANALYSIS (IA)

An IA will be performed for each cohort after the first 23 patients for mCRPC cohorts or the first 20 patients for NSCLC cohorts in the Phase 2 part have completed 6 cycles. The interim analysis may be conducted earlier if the required number of responders proceeding to Phase 2 Stage 2 is achieved.

The analysis will include the following parameters/analyses (defined in Section 2.1): response rate, demographics and baseline characteristics, prior or concomitant medication, AEs (TEAE, death, SAE, TEAE leading to discontinuation, IAR, AESI), and laboratory variables (abnormality of hematological and chemistry test). If needed, more data will be analyzed to inform the futility decision including additional efficacy, PK, and biomarker.

4 DATABASE LOCK

The database will be locked when clinical review of the database has been completed and all critical queries have been resolved.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS® version 9.4 or higher.

6 REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

2. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, Antonarakis ES, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34:1402-18.

3. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18:e143-52.

4. Alexander Kratz, Maryjane Ferraro, Patrick M. Sluss and Kent B. Lewandrowski, MD. Laboratory reference values.

7 LIST OF APPENDICES

Appendix A Generic ranges for hematological and biochemistry parameters

Table 6 - Generic ranges for hematological parameters

Test	Gender	Unit	Lower/Upper limit of normal
Hemoglobin	F	g/L	120 - 160
Hemoglobin	M	g/L	135 - 175
Lymphocytes		109/L	1-2
Neutrophils		109/L	1.8 – 3.15
Platelets		109/L	150 - 350
Leukocytes		109/L	4.5 - 11
Eosinophils		109/L	0 – 0.4
Basophils		109/L	0 – 0.15
Monocytes		109/L	0.18 – 0.5
Hematocrit	M	Ratio	0.41 -0.53
Hematocrit	F	Ratio	0.36 – 0.46
Erythrocytes	F	1012/L	4 – 5.2
Erythrocytes	M	1012/L	4.5 -5.9
INR		ratio	0.8 -1.2

Based on Kratz et al.((4)

Table 7 - Generic ranges for biochemistry parameters

Test	Unit	Lower – Upper limit of normal
Albumin	g/L	35 - 55
BUN	mmol/L	3.6 – 7.1
Calcium	mmol/L	2.2 - 2.6
Chloride	mmol/L	80 - 115
Corrected calcium	mmol/L	2.2 – 2.6
Glucose	mmol/L	3.9 - 7
Bicarbonate (HCO3)	mmol/L	22 - 29
Carbon dioxide	mmol/L	21 - 30
Potassium	mmol/L	3.5 - 5
Magnesium	mmol/L	0.8 - 1.2
Sodium	mmol/L	136 - 145
Phosphate	mmol/L	1 - 1.4
Protein	g/L	55 - 80
Urea	mmol/L	3.6 - 7.1

ACT15319 16.1.9 Statistical analysis plan

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]		