Sponsor Name: Navitas Life Sciences GmbH
Short Title of Study: Long-Term Retention of Gadolinium in Bone
Statistical Analysis Plan (SAP)
Sponsor Study No.: ALS-Gd64/001
Version No.: Final 1
Date:31JUL2019
NLS Study No.: 665

STATISTICAL ANALYSIS PLAN

Study Title:	Exploratory evaluation of the potential for long-term retention of Gadolinium (Gd) in the bones of patients who have received Gadolinium based Contrast Agents (GBCAs) according to their medical history.
Sponsor Identification:	Navitas Life Sciences GmbH Hahnstrasse 70 60528 Frankfurt, Germany
Phase:	Post Authorisation Study / Phase IV
Active ingredients of products under evaluation:	Gadobutrol, Gadodiamide, Gadopentetic acid, Gadoteric acid, Gadoversetamide, and Gadoxetic acid
Study Number:	ALS-Gd64/001
NLS Study Number:	665
Responsible Biostatistician:	Sonja Ikemeyer-Fuchs Biostatistician Navitas Life Sciences GmbH Hahnstraße 70 D-60528 Frankfurt a.M. Tel.: +49-(0)69-66 80 30 0 Fax: +49-(0)69-66 80 30 29 E-mail: Sonja.Ikemeyer-Fuchs@navitaslifesciences.com
Date of SAP:	31JUL2019
Version:	Final 1
Scope:	Final Analysis

Sponsor Name: Navitas Life Sciences GmbH
Statistical Analysis Plan (SAP)
Version No.: Final 1

Date:31JUL2019

Short Title of Study: Long-Term Retention of Gadolinium in Bone
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	Marty Boom Managing Director	02 Aug 2019 Date (DD MMM. YYYY)
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02/AUG/2019
Date (DD MMM. YYYY)

1 TABLE OF CONTENTS

2 DOCUMENT HISTORY

Version	Date	Change to previous version
Final 1	31JUL2019	No previous version

3 ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomic therapeutic chemical classification
BLQ	Below the Limit of Quantification
CHMP	Committee for Medicinal Products for Human Use
CPS	Counts per Second
CSP	Clinical Study Protocol
CI	Confidence interval
CRF	Case report form
CRO	Clinical research organization
%CV	Coefficient of Variation (of geometric Mean) %
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FPFV	First Patient First Visit
FAS	Full analysis set
Geomean	Geometric Mean
Gd	Gadolinium
GBCA	Gadolinium based Contrast Agent
GLP	Good Laboratory Practices
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International conference on harmonization
ICP-AES	Inductively Coupled Plasma - Atomic Emission Spectrometry
ICP-MS	Inductively Coupled Plasma - Mass Spectrometry
IFC	Informed Consents
ITT	Intent-to-treat
IP	Investigational product
IMP	Investigational medicinal product
LLOQ	Lower Limit of Quantification
LPLV	Last Patient Last Visit
MAH	Marketing Authorization Holder
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
MD	Medicine Doctor
Min	Minimum
MSc	Master of Science
N	Number of non-missing observations
Nmiss	Number of missing observations

NSF	Nephrogenic Systemic Fibrosis
PPS	Per protocol set
PT	Preferred term
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
SD (geometric)	Geometric standard deviation (re-transformed standard deviation of the logarithms)
SOC	System organ class
SOP	Standard operating procedure
TLF	Tables, Listings and Figures
V	Visit

4 DOCUMENTS

Amended Clinical Study Protocol (CSP) Version 4.0, dated 29 April 2016.
Abbreviated Report on the interim analysis, Version 1.0, dated 08 NOV 2018.

5 INTRODUCTION

Study ALS-Gd64/001 to evaluate the potential for long-term retention of Gadolinium (Gd) in human bone and skin after administration of Gadolinium based Contrast Agents (GBCAs) and co-factors that may increase the risk of nephrogenic systemic fibrosis (NSF) was requested by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA). The study is explorative in nature and will deliver descriptive data on the potential for long-term retention of Gadobutrol, Gadodiamide, Gadopentetic acid, Gadoteric acid, Gadoversetamide, and Gadoxetic acid in human bone and skin.

This Statistical Analysis Plan (SAP) is based on the relevant sections of the amended CSP and includes also the Tables, Listings and Figures (TLF) Specifications. It describes in more detail how the analyses are to be performed and presented.

6 STUDY OBJECTIVES

6.1 Primary Objectives

To prospectively explore the potential for long-term retention of Gd in bones in subjects who have received a single dose of GBCA or multiple doses of the same GBCA, with moderate or severe renal impairment function or stable normal renal function at the time of GBCA injection.

6.2 Secondary Objectives

- To evaluate skin samples for concentration of Gadolinium
- To evaluate bone and skin samples for concentrations of calcium, phosphorus, sodium, iron, zinc and potassium
- To evaluate skin samples for any dermatopathological changes that may be associated with NSF
- To describe potential co-factors for NSF, susceptibility factors and drug treatments with potential impact on bone metabolism

7 STUDY DESIGN

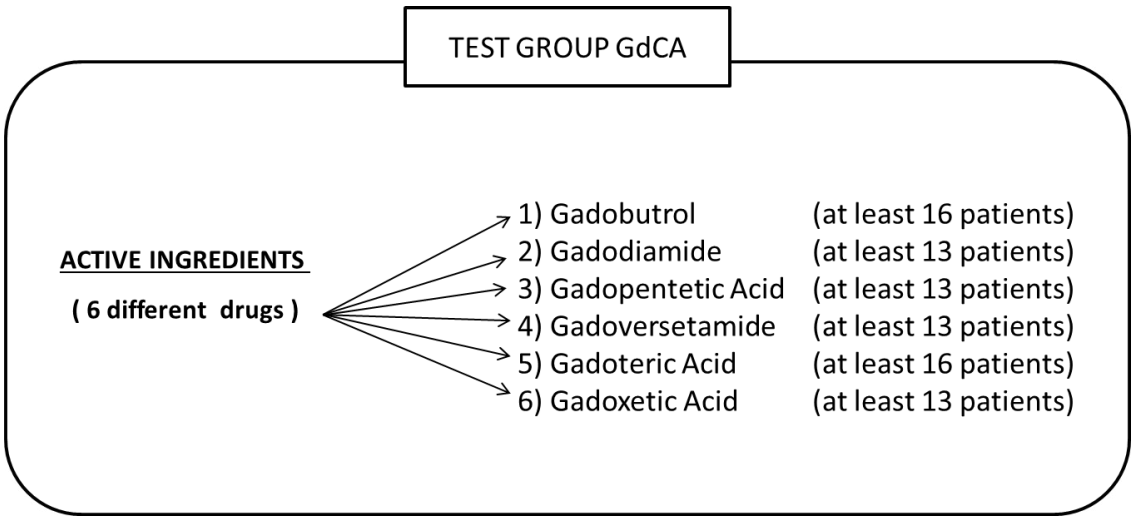
7.1 Overview

This is a multicenter, retrospective, prospectively interventional and exploratory, post authorization study, which is conducted globally evaluating the potential for long-term retention of Gd in bones of subjects who received single or multiple doses of GBCAs. The study is retrospective with respect to GBCA administration (no GBCA will be administered to subjects during the study by the investigator), prospective with respect to bone sample collection (taken from surgically removed bone) and both, prospective and interventional regarding skin sample collection. Skin sampling is required for both dermatopathological assessment and quantification of Gd.

The study population consists of subjects undergoing an orthopedic procedure, provided that the required amount of trans-operatory collection of bone and skin as defined per-protocol is feasible. All inclusion criteria and no exclusion criteria should be met (please refer to sections 5.1.3, 4.1 and 4.2 of the CSP). Subjects must be aged at least 18 years (or older if required by local regulations) and have received GBCA at least 1 month prior to surgery (test group). Additionally, a group of subjects undergoing hip or knee replacement surgery who have not received GBCA is enrolled (control group).

A minimum of 99 evaluable subjects from centers in America, Europe and Asia have to be enrolled. In the test group at least 84 subjects should be enrolled and in the control group at least 15 subjects should be enrolled. The products assessed should be GBCAs which include one of the active ingredients Gadobutrol, Gadodiamide, Gadopentetic acid, Gadoteric acid, Gadoversetamide or Gadoxetic acid. In the test group at least 13 subjects should be included per GBCA active ingredient group for Gadodiamide, Gadopentetic acid, Gadoversetamide, and Gadoxetic acid and at least 16 subjects should be included per GBCA active ingredient group for Gadobutrol and Gadoteric acid.

Figure 1: Target number of subjects per GBCA



Furthermore, documentation of stable renal function prior to administration of the GBCA is required, and renal function must have been assessed at least once within approximately 3 months prior to GBCA injection. Section 8.2 will describe the stratification plan for all subjects in detail.

The recruitment has started with first subject enrolled in May 2013. Due to difficulties in finding the eligible subjects the recruitment has been extended several times resulting in total recruitment duration of 68 months (from May 2013 until December 2018). End of study for the individual subject is follow-up visit 2 (visit 4) taking place, approximately within 10-14 days after the orthopedic surgery procedure (e.g. hip or knee replacement surgery) at the time of potential stitch removal under normal healing conditions. A detailed schedule of study procedures and assessments is presented in the flow chart of section 7.2.

The study period for each subject includes the scheduled bone and skin sample collection in conjunction with a medically indicated orthopedic surgery procedure. If the subject is scheduled for a second orthopedic surgery procedure (e.g. hip or knee replacement surgery) to be performed within the study period, the subject can continue to participate in the study, provided that the required amount of trans-operatory collection of bone and skin as defined per-protocol is feasible during the second procedure. A second bone and skin sample shall be collected during the second scheduled orthopedic procedure. The overall study period will not be extended in order to obtain the second bone and skin sample collection.

Handling and analysis of trabecular and cortical bone and skin samples will be performed under blinded conditions at central laboratories**.**

7.2 Study Flow-Chart

Table7.2.1: Schedule of Procedures and Assessments

	Visit 0 Screening Visit	**Visit 1 (V1) Baseline** (within 3 days prior to surgery)	**Visit 2 (V2) 1st surgery** (day 0)	**Visit 3 (V3) Follow-up 1** (3-5 days after surgery)	**Visit 4 (V4) Follow-up 2** (approximately within 10-14 days after surgery)	**If applicable: Subjects receiving a 2nd surgery only**			
						Visit 5 (V5)* Baseline (within 3 days prior to surgery)	**Visit 6 (V6)* 2nd Surgery** (within study timeframe)	**Visit 7 (V7)* Follow-up 3** (3-5 days after surgery)	**Visit 8 (V8)* Follow-up 4** (approximately within 10-14 days after surgery)
Subject information and signature on Medical Data Release Form	x								
Subject information, written informed consent		x							
Written informed re-consent, if applicable						x			
Demographic data	x								
Diagnosis and medical history		x				x			
Inclusion and exclusion criteria	x	x				x			
Renal status (retrospective with regard to GBCA administrations)	x								
GBCA history / verification of GBCA history	x	x	x			x	x		
Connection to IWRS for stratified enrolment		x							
Concomitant diseases and therapies	x	x	x	x	x	x	x	x	x
Study-specific parameters:									
Bone sample collection			x				x		
Skin sample collection			x				x		
Visual check of wound/scar				x	x			x	x
Adverse events		x	x	x	x	x	x	x	x

* Additional visit for subjects scheduled for second orthopaedic surgical procedure within study timeframe In case no second surgery is planned at completion of visit 2, the study ends with the end of the follow-up visit 2 (V4)

7.3 Parameters

7.3.1 Evaluation Parameters

Primary Parameter

- Total Gd concentration in trabecular bone in µg/g
- Total Gd concentration in cortical bone in µg/g

Secondary Parameter

- Total Gd concentration in skin tissue in µg/g
- Gd concentration in bone (trabecular and cortical) and skin as a function of time elapsed between GBCA injection and surgery
- Number of single (one injection of standard dose) or multiple (more than one injection or one injection with higher than standard) doses
- Cumulative dose of GBCA i.e total mmol administered prior to surgery.
- Time elapsed between most recent administration of GBCA [month] and surgery.
- Time of cumulative GBCA doses [months]
- Time intervals of dosing
- eGFR [ml/min/1.73 m^2]
- Potential co-factors for NSF and susceptibility factors, based on the following data and in the limit of their availability in medical history of the patients:
    - eGFR;
    - cumulative dose of GBCA,
    - co-existing vascular, thrombotic and/or pro-inflammatory events
    - serum concentrations of calcium, phosphorus, sodium, iron, potassium and zinc
    - Any event which may have led to Iron mobilization, including concomitant iron drug
    - Cumulative dose of erythropoietin [IU/L]
    - T4 and TSH
- Concomitant drug treatments with potential impact on bone metabolism:
    - biphosphonates
    - estrogens
    - calcitonin
    - calcitriol
    - fluoride salts
    - vitamin D
    - corticosteroids
- Concentration of Ca, P, Na, Zn, K and Fe in skin and in tissue of both trabecular and cortical bone, determined by ICP-MS
- Clinical histological evidence of NSF (determined by an experienced dermatopathologist).
- Subjects who have undergone 2 surgeries

7.3.2 Safety Parameters

- Adverse event (AE) description
- Onset date/time of AEs
- Resolution date/time of AEs
- Relationship (possibly, probably or certainly related)
  - related to the orthopedic surgery (bone resection included)
  - related to the skin biopsy
  - related to GBCA exposure in the past (e.g. NSF signs after enrolment)
  - related to other health conditions of the subject
- Intensity (mild, moderate, severe)
- Serious (yes, no)
  Description of the serious adverse events (SAE)
  NSF-like events will be considered medically important events, and thus are serious AEs
- Expectedness (yes, no)
- Outcome of AEs (resolved, resolved with sequelae, not recovered, fatal, unknown)
- Concomitant diseases and medical history
- Previous and concomitant medication

8 GENERAL STATISTICAL CONSIDERATIONS

Primary and secondary variables will be analyzed descriptively. No formal hypothesis testing is planned.

8.1 Descriptive Statistics

The following descriptive statistics will be calculated for continuous data and for ordered categorical data (ordinal data) if applicable:

Summary statistics are displayed with the following digits:

Description	**Characteristic**	**Number of decimal places**
Count	n	0
N (number of non-missing measurements)	N	0
Arithmetic Mean	Mean	As in source + 1
Geometric Mean	GM	As in source + 1
Standard Deviation	SD	As in source + 1
Geometric standard deviation	GSD	As in source + 1
Corresponding %CV	%CV	2
Minimum	Min	As in source
Median	Median	As in source + 1
Maximum	Max	As in source
Percentage relative to N	%	1 *

* Number of decimal places can be two, if necessary. All table percentages should be rounded to one decimal place if not stated otherwise. If the rounded percentage is 0.0%, then the percentage should be printed as < 0.1%.

For ordered categorical data and nominal data, absolute and relative frequencies (in %) will be calculated. A Missing category should be added to any parameter for which information is not available for any subjects and included in all calculations (%).

All relevant medical history conditions and concomitant diseases will be coded in MedDRA and summarized by system organ class and preferred term. The version of the utilized dictionary will be presented as part of the provided tables and listings.

Any disease starting at the date of informed consents or later will be classified as concomitant disease.

All prior and/or concomitant medications and therapies will be coded according to the World Health Organization (WHO) Drug Dictionary according to WHO Preferred Term (ATC level 5). Subjects taking the same medication multiple times will be counted once per medication. The version of the utilized dictionary will be presented as part of the provided tables and listings.

All medication and therapies starting at the date of informed consents (IFC) or later will be classified as concomitant medications and concomitant therapies, whereas, all concomitant medications and therapies starting before the date of IFC will be classified as previous medications and previous therapies. Any previous medications or previous therapies that is still ongoing will be classified as both prior and concomitant medications and prior and concomitant therapies.

All AEs will be presented by primary system organ class and preferred term and sorted alphabetically if not stated otherwise.

All data will be presented in the subject data listings.

If either table or listing does not include any observation, then the following placeholder will be used: "NO DATA CONTRIBUTED TO THIS TABLE / LISTING".

8.2 Grouping and Assignments

Statistical tables will be calculated for all GBCA groups pooled as well as each GBCA group separately and the control group. These will be further stratified according to renal function categories, single/ multiple doses (2 groups), and the combination of "renal function with "single / multiple doses".

The CSP did intend to have three different renal function categories:

- Subjects with stable severe renal impairment (eGFR < 30 ml/min/1.73 m^2)
- Subjects with stable moderate renal impairment (eGFR within the range 30 to 60 ml/min/1.73 m^2)
- Subjects with stable normal renal function (eGFR > 60 ml/min/1.73 m^2)

However, in order to improve recruitment protocol, amendment 3 and finally CSP v.4.0 were established and introduced a change from three renal function groups into two renal function groups. The two subgroups severe renal impairment and moderate renal impairment were combined into "at least moderate impaired renal function" (eGFR <= 60 ml/min/1.73 m2) whereas the definition for stable normal renal function (eGFR > 60 ml/min/1.73 m^2) was maintained. As a consequence, recruited subjects showed mostly" moderate" or "normal" impaired renal function, whereas "severe" impaired renal function is very rare. Due to this small sample size (3 subjects in SAF), "severe" and "moderate" impairment will be analyzed as a combined group (at least moderate impaired renal function) in the following. This approach was also followed during the IA and displayed in the IA-CSR.

This study is a multinational, multicenter study. However, due to the small sample size of each stratification group, results will not be further stratified by country or center.

8.2.1 Group and Stratification Variables

- GBCA test group or control
- Renal function category (at least moderate impairment (eGFR <= 60 ml/min/1.73 m^2), stable normal renal function (eGFR > 60 ml/min/1.73 m^2)
- Single (one injection of standard dose) or multiple (more than one injection or one injection with higher than standard) doses of GBCA administered
- Combination of "renal function with "single / multiple doses"
- Elapsed time from first dosing of GBCA until surgery (cumulative dose of GBCA) will be classified and will also be used for stratification.

8.2.2 Stratification Plan

GBCA Test Group

Table 1 and Figure 2 describing targeted number and stratification of subjects for each GBCA group by renal functional status. The numbers reflect the enrolment targets after the introduction of CSP v.4.0. The groups of severe and moderate impaired renal function are combined as explained above **and** in the section 10.

Table 1: Target number of subjects per GBCA and renal function status

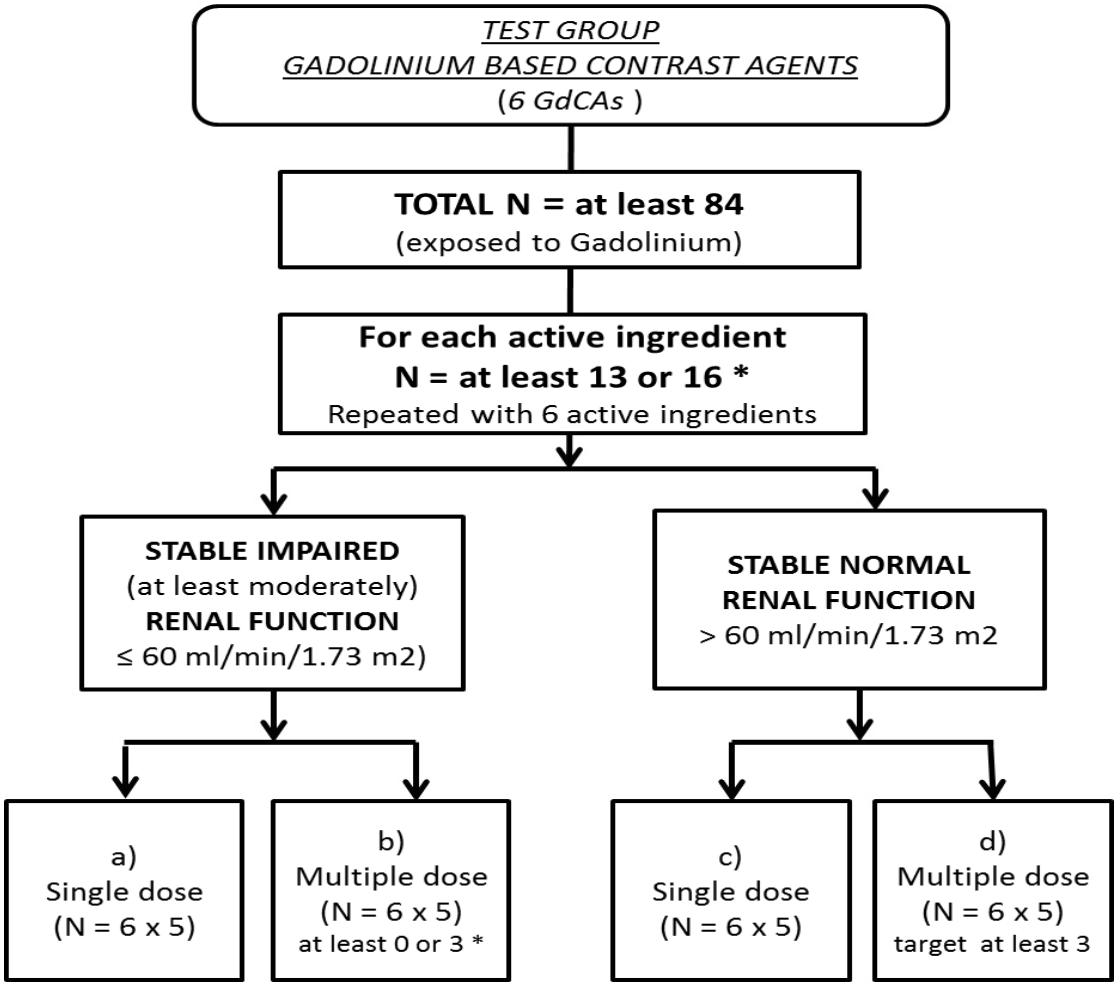
GBCA	Impaired renal function (at least moderate impairment, eGFR ≤ 60 ml/min/1.73 m^2)		Stable normal renal function eGFR > 60 ml/min/1.73 m^2)	
	Single dose	Multiple dose	Single dose	Multiple dose
Gadobutrol	5	3 to 5*	5	3 to 5**
Gadoteric acid	5	3 to 5*	5	3 to 5**
Gadodiamide	5	0 to 5*	5	3 to 5**
Gadopentetic acid	5	0 to 5*	5	3 to 5**
Gadoversetamide	5	0 to 5*	5	3 to 5**
Gadoxetic acid	5	0 to 5*	5	3 to 5**

* Subjects should be recruited to the Gadodiamide, Gadopentetic acid, Gadoversetamide, and Gadoxetic acid subgroups throughout the study duration up to a maximum of 5, but there is no minimum requirement to reach a specific number of subjects in this subgroup to achieve study completion. At least 3 subjects and a maximum of 5 subjects are required for Gadobutrol and Gadoteric

acid. If the target of 3 subjects is reached, but the study has not yet completed, then recruitment to this subgroup should be continued during the remaining study time.

** At least 3 subjects are required for this subgroup. If the target of 3 subjects is reached, but the study has not yet completed, then recruitment to this subgroup should be continued during the remaining study time, stopping when until 5 subjects have been recruited to this subgroup, or when all other subgroups have reached their minimum target for recruitment, whichever comes first.

Figure 2: Stratification of subjects for recruitment purposes by renal functional status and GBCA dosing:



* Depending on the GBCA subgroup

Control Group

For the control group at least 5 subjects with normal renal function and up to 10 subjects with at least moderate impaired renal function have to be recruited.

8.3 Analysis Set

Analysis Set	Definition
Screening population	All subjects who entered the study
Safety analysis set (SAF)	All subjects who have undergone the planned orthopedic surgical procedure
Full analysis set (FAS)	All subjects in the SAF for whom Gd measurements from the bone are available
Per protocol set (PPS)	All subjects in the FAS who meet the defined requirements of GBCA treatment history, all inclusion and exclusion criteria, and whose tissue samples yield data for Gd in bone (trabecular as well as cortical) and skin. The evaluability of subjects /samples shall be assessed by a blinded data review prior to final unblinding and analysis.

8.4 Protocol Deviation

The relevant protocol deviations (PD) have to be defined by a systematic data review prior to database closure. For this purpose, PDs that occurred during the study such as deviations of inclusion/exclusion criteria or forbidden concomitant medications will be assessed as ‘major’ or ‘minor’ depending on their potential to interfere with the objectives of the study. Listings will be prepared to show the eligibility of all subjects. Comprehensive justification for the classification of a PD as “major” will be given in the integrated clinical study report.

Major protocol deviations and the assessment of analysis sets will be defined during last data review before data base closure. All definitions given in the Minutes of the Final Data Review will be considered in the analysis.

Due to the fact, that the laboratory data for all subjects included in the IA had to be unblinded, these subjects have already been classified before the IA evaluation with regard to PDs.

The list of protocol deviations will be reviewed by the sponsor and finalized before locking the database. The sponsor will identify major protocol violations which will lead to exclusion of subjects from the PPS. Major protocol violations excluded from PPS will be flagged in the protocol violation listing.

8.5 Data Handling

There will be no imputation of missing data. All data will be analyzed as they appear in the data base.

Since the geometric mean (the retransformed mean of the logarithmized values) and CV% cannot be calculated in the presence of zero values, the values BLQ were implemented in the IA analysis by half the LLOQ (i.e. 0.025) instead of zero for the calculation of the descriptive statistics. This approach will also be

used for the final analysis. Therefore, values below the limit of quantification (LLOQ) will be replaced by half of the LLOQ (i.e 0.025) instead of zero for the calculation of the descriptive statistics. For adverse events the following rules will be applied:

- AEs with unknown onset date/time will be counted as treatment emergent AEs.
- AEs with unknown end date/time will be counted as an ongoing AE.
- AEs with unknown relationship to GBCA will be counted as related in AE summary tables.
- If for the calculation of a time period the full date format ddmmmyyyy is needed, missing entries will be imputed as follows:
  - Missing day in start date of a time period is imputed by the first day of the month;
  - Missing day in stop date of a time period is imputed by the last day of the month;
  - Missing month in start date of a time period is imputed by January of the year;
  - Missing month in stop date of a time period is imputed by December of the year;
  - Missing year is not imputed.

8.6 Sample Size Calculation

Due to the exploratory nature of the study, the sample size was not determined based on formal statistical consideration, but rather on the feasibility of conducting the study as a whole. The study is intended to be analyzed descriptively. No formal hypothesis testing is planned.

There are six groups for active GBCA ingredients (Gadobutrol, Gadodiamide, Gadopentetic acid, Gadoteric acid, Gadoversetamide, and Gadoxetic acid). In each group, two categories of renal function (stable (normal) renal function (eGFR > 60 ml/min/1.73 m^2) versus at least moderate impaired renal (<=60 ml/min/1.73 m^2) and two subgroups of dosing of GBCA (single / multiple) are to be evaluated.

Per active GBCA ingredient the recruitment targets are defined as follows:

- 5 subjects for stable normal renal function (eGFR > 60 ml/min/1.73 m2) and single dose
- at least 3 subjects and up to 5 subjects for stable normal renal function and multiple doses
- 5 subjects for at least moderate impaired renal function (eGFR <=60 ml/min/1.73 m2) and single dose
- up to 5 subjects for at least moderate impaired renal function (eGFR <=60 ml/min/1.73 m2) and multiple doses. For Gadobutrol and Gadoteric acid, at least 3 subjects are required. For Gadodiamide, Gadopentetic acid, Gadoversetamide, and Gadoxetic acid, there is no requirement to reach a specific number of subjects to achieve study completion.

The total target number of subjects enrolled in these groups will be at least 84.

The number of subgroups in the GBCA-naïve population is two according to renal function category (i.e. at least moderate impairment, and stable normal renal function) and should follow the distribution of the GBCA population. At least five subjects with stable normal renal function (eGFR > 60 ml/min/1.73 m^2) and at least 10 subjects with at least moderate impaired renal function (eGFR <=60 ml/min/1.73 m^2) will

be enrolled. Therefore, the total target number of GBCA-naïve subjects enrolled will be at least 15. Consequently, a minimum of 99 subjects in total shall be included in the study.

8.7 Interim Analysis

At the request of the EMA, an interim analysis was to be carried out on all subjects enrolled in the single dose subgroups for Gadobutrol, Gadoteric acid, Gadodiamide, and Gadopentetic acid once at least three subjects had been recruited to the single-dose subgroups for the 4 agents as well as on all subjects of the control group (naïve subjects).

A total of 55 subjects were eligible for the IA. Due to the fact, that the laboratory data for these subjects had to be unblinded, these subjects have already been classified before IA evaluation with regard to PDs. Since one subject had no concentration data available, only 54 subjects were included in the SAF.

To determine the Gd concentration in bone (trabecular and cortical) and skin (expressed as µg Gd / g) the IA based on the SAF and Gd concentrations was descriptively evaluated by:

- Renal function status: stable normal renal function (eGFR > 60 ml/min/1.73 m^2),
  at least moderate impaired renal function (<=60 ml/min/1.73 m^2)
- GBCA: Each of the 4 GBCAs (Gadobutrol, Gadoteric acid, Gadodiamide, and Gadopentetic acid) and control

No statistical tests have been calculated.

All data used in the interim analysis have been listed. All listings including subject identifier, GBCA type, renal function, and have been sorted by GBCA type, renal function, and subject identifier. Study investigational sites and analytical laboratories have been blinded to the IA results.

Details on the IA evaluation have been described in the interim SAP and the Abbreviated Interim Analysis Report, Version Final 1.0, dated 20181108.

8.8 Subgroup Analysis

This study was performed as a multinational multicenter study. Due to the small sample size of each stratification group, results will not be further stratified by age or country or center and nor special subgroup analyses will be performed.

The subjects who have undergone two surgeries on study will be analyzed as a subgroup, at least for Gd concentration in bone and skin. Descriptive statistics will be calculated for the difference of Gd concentration in bone (trabecular and cortical) and in skin at the time of first and the time of second surgery. Since the number of subjects in this subgroup is so low, no stratification will be performed.

8.9 Definitions and Derived Variables

Variable / Term	Definition / Way of calculation
Test group	Refers to subjects with GBCA exposure
Control	Includes GBCA naïve subjects
Stable normal renal function	Stable normal renal function (eGFR > 60 ml/min/1.73 m^2),
Impaired renal function	Impaired renal function (eGFR <=60 ml/min/1.73 m^2) The groups of sever and moderate impaired renal function are combined as explained in the section 10.
Single dose	Only one application of GBCA (0.1 mmol per kg body weight for Gadobutrol, Gadoteric acid, Gadodiamide, and Gadopentetic acid; 0.025 mmol per kg body weight for Gadoxetic acid)
Multiple dose	More than one application of GBCA or one injection with higher than approved standard dose (0.1 mmol per kg body weight for Gadobutrol, Gadoteric acid, Gadodiamide, and Gadopentetic acid; 0.025 mmol per kg body weight for Gadoxetic acid))
Time between most recent administration of GBCA [month] and surgery	= (Date of surgery – date of most recent GBCA administration +1 day) / 30.25
Time of cumulative GBCA doses [month]	= (Date of surgery – date of first GBCA administration +1 day) / 30.25
Cumulative dose of GBCA (mmol)	= Sum of all administrated GBCA doses
Cumulative dose of erythropoietin [IU/L]	= Sum of all administrated erythropoietin doses

8.10 Statistical Software

All statistical analyses will be performed with SAS®, Version 9.4 or later. Working instructions are printed in yellow italic text below the shells, e.g.: *Repeat table for PPS (14.2.2).*

9 STATISTICAL ANALYSES

The statistical analysis will be carried out for all GBCA groups pooled as well as each GBCA group separately and the control group. They will be further stratified according to renal function category (2 groups), single / multiple doses (2 groups), and the combination of "renal function with "single / multiple doses".

All tables will be programmed for the control group, all GBCA groups pooled as well as for each GBCA group separately. Each table will be presents by all stratification for the renal function categories (2 groups = 2 columns). Repeat tables will be produced by treatment/renal function and dose (single / multiple doses) combined.

Because standard point estimates may be biased when the total number of BLQ values is large (such as when it exceeds 1/3 of the total), the descriptive analysis should only to be calculated if at least 2/3 of the individual data had been measured and found to be above the LLOQ (rationale based on PhUSE_CSS_WhitePaper_PK_final_25March2014.pdf).

9.1 Subject Disposition

Subject disposition will be tabulated with number and percentages of subjects screened, enrolled, completed according to the protocol, number of surgeries, lost to follow-up or discontinued prematurely. The subjects who prematurely discontinued the study and the reasons for their discontinuation will be presented. Screening failures will be excluded from the analysis but listed in subject data listings.

9.2 Demographic Data and Baseline Characteristics

All Demographic data and baseline characteristics will be displayed for the SAF, FAS and PPS (see definition 8.3).

Demographic data and baseline characteristics will be analyzed using descriptive statistics in summary (mean, SD, median, min and max) or frequency (number and percentage) tables. The following parameters will be analyzed:

- Gender
- Age (years)
- Height (cm)
- Weight (kg)
- Historical use of gadolinium based contrast agent (GBCA)
- Diagnosis of qualifying study indication (affected joint, diagnosis, duration, severity of diagnosis)

9.3 Medical History and Concomitant Diseases

For the SAF medical history conditions and concomitant diseases frequency counts will be summarized by system organ class and preferred term.

9.4 Previous and Concomitant Medications

For the SAF previous and/or concomitant medications and therapies will be summarized in a frequency table, starting at the date of informed consents or later.

9.5 Orthopedic Surgery - Bone and Tissue Sampling

For the SAF number and frequencies will be provided by first and second surgery for:

- Type of surgery (hip replacement surgery, knee replacement surgery shoulder replacement surgery and other orthopedic surgery)
- Surgery site (right,left, other)
- Sample taken (yes, no)
  - Trabecular bone
  - Cortical bone
  - Skin (for bioanalytics)
  - Skin (for histopathology)

9.6 Analysis

9.6.1 Primary Analysis

The primary evaluation parameters Gd concentration in bone (trabecular and cortical) will be descriptively tabulated for the control group and each of the 6 GBCAs (Gadobutrol, Gadodiamide, Gadopentetic acid, Gadoteric acid, Gadoversetamide, and Gadoxetic acid) and presented by renal function status: stable normal renal function (eGFR > 60 ml/min/1.73 m^2) and at least moderate impaired renal function (<=60 ml/min/1.73 m^2). For mean, SD and %CV the geometric equivalents will be calculated.

The primary analysis will be performed on the full analysis (FAS) and the per protocol set (PPS) (see definitions 8.3).

No statistical tests will be calculated.

9.6.2 Secondary Analysis

The secondary evaluation parameter Gd concentration in skin (expressed as µg Gd /g) will be analyzed for the FAS analogously to the primary parameter.

For the following secondary parameter number and percentages or arithmetic summery statistics will be presented for the FAS where applicable.

- Time elapsed between most recent administration of GBCA and surgery in month
- Time of cumulative GBCA doses [month]
- Potential co-factors for NSF and susceptibility factors, based on the following data and in the limit of their availability in medical history of the subjects:
  - eGFR
  - cumulative dose of GBCA
  - co-existing vascular, thrombotic and/or pro-inflammatory events
  - serum concentrations of calcium, phosphorus, sodium, iron, potassium and zinc

- any event which may have led to iron mobilization, including concomitant iron drug
- cumulative dose of erythropoietin
- T4 and TSH.

- Concomitant drug treatments with potential impact on bone metabolism: biphosphonates, estrogens, calcitonin, calcitriol, fluoride salts, vitamin D, corticosteroids.
- Concentration of Ca, P, Na, Zn, K and Fe in skin and in tissue of both trabecular and cortical bone determined by ICP-MS.

No statistical tests will be calculated.

9.7 Adverse Events

Safety analysis will be performed for the SAF and will be included the investigation of adverse events (AEs), serious adverse events (SAEs) and adverse drug reactions (ADRs) as well as serious adverse drug reactions (SADR)s.

For all AEs occurring after enrolment, a summary containing the following counts and percentages of subjects will be presented by treatment:

- Number of AEs
- Number and percentage of subjects with at least one AE
- Number and percentage of subjects with at least one AE:
  - related to the orthopedic surgery (bone resection included)
  - related to the skin biopsy
  - related to GBCA exposure in the past (e.g. NSF signs after enrolment)
  - related to other health conditions of the subject
- Number and percentage of subjects with expectedness for potential AEs in response to GBCA exposure in the past (e.g. NSF signs after enrolment)
- Number and percentage of subjects with AEs by intensity
- Number and percentage of subjects with SAEs
- Number and percentage of subjects who died
- Number and percentage of subjects who discontinued due to AE

Further, all AEs, SAEs, ADRs and SADRs will be summarized in a frequency table by MedDRA system organ class and preferred term. The version of the utilized dictionary will be presented as part of the provided tables and listings.

9.8 Other Parameters

Not applicable.

10 DEVIATION FROM THE STUDY PROTOCOL

The planned analysis will be performed according to the study protocol, its amendments and this statistical analysis plan. If there are contradictions between the study protocol or its amendments and this statistical

analysis plan, the analysis will be performed according to this analysis plan. Any deviation from the planned analysis according to the study protocol has to be described in the integrated report.

The differences between study protocol and statistical analysis plan are summarized in the following table:

Change	**Study protocol**	**Statistical analysis plan** Will be changed to:
Wording in CSP	GdCA	GBCA
	Impaired renal function (eGFR <30 ml/min/1.73 m^2 (severe) and ≥30 to <=60 ml/min/1.73 m^2 (moderate))	At least moderate impaired renal function (eGFR <=60 ml/min/1.73 m^2) In order to improve recruitment CSP amendment 3 introduced a change from three renal function groups into two renal function groups. The two subgroups severe renal impairment and moderate renal impairment were combined into “at least moderate impaired renal function” (eGFR <= 60 ml/min/1.73 m2) whereas the definition for stable normal renal function (eGFR > 60 ml/min/1.73 m^2) was maintained. As a consequence, recruited subjects showed mostly” moderate” or “normal” impaired renal function, whereas “severe” impaired renal function is very rare. Due to small sample size (3 patients in SAF), “severe” and “moderate” impairment.needs to be combined
Wording in CSP used in section 8.1.2	Statistical tables will compare all GdCA groups pooled as well as each GdCA group separately versus the control group.	Statistical tables will be calculated for all GBCA groups pooled as well as each GBCA group separately and the control group.

Change	Study protocol	Statistical analysis plan Will be changed to:
	They will be further stratified according to renal function category (3 groups), single / multiple doses of all subjects (2 groups), and the combination of "renal function with "single / multiple doses".	They will be further stratified according to renal function category (2 groups), single / multiple doses of all subjects (2 groups), and the combination of "renal function with "single / multiple doses".
	The number of subgroups in the GdCA-naïve population is 3 according to renal function category (i.e. severe or moderate impairment, and stable normal renal function).	The number of subgroups in the GdCA-naïve population is 2 according to renal function category (at least moderate impairment, and stable normal renal function).

10.1 Further Deviations

In the IA report as compared to the IA SAP is the replacement of values BLQ defined by half of the LLOQ (i.e 0.025) instead of zero for the calculation of the descriptive statistics because in the presence of zero values, the geometric mean (the re-transformed mean of the logarithmized values) and %CV cannot be calculated. This procedure will also apply here (see Section 8.5)

11 SOPS FOR ANALYSIS AND REPORTING

Navitas Life Sciences standard operating procedures are to be used for this analysis.

The following SOPs are to be used

Title
ICH Topic E9(CPMP/ICH/363/96) "Note for Guidance on Statistical Principles for Clinical Trials"
NLS.STAT.ALL.SOP.005 – Preparation of SAP
NLS.STAT.ALL.SOP.007 – Create raw datasets, derived datasets and archive data
NLS.STAT.ALL.SOP.009 – Perform Statistical Analysis and Generate Tables, Graphs and Listings
NLS.STAT.ALL.SOP.011 – Validating SAS programs

The structure of post-text-tables and the appendices will be in accordance with the ICH guideline E3.

12 DATABASE LOCK AND UNBLINDING

The SAP will be finalized prior to database lock or any unblinding of study team members. After the data cleaning process is finalized according to the data management plan (DMP) and the assignment of subjects to the analysis sets is agreed and signed by the sponsor, the study data base will be locked. SAS datasets will be extracted from the study data base as described in the DMP.

13 REFERENCES

European Medicines Agency (EMA). Guideline on bioanalytical method validation (2011). http://www.ema.europa.eu/docs/en_GB/document_library/Scientificguideline/2011/08/WC500109686.pdf. Accessed 24 Oct 2018. Further references are given in the study protocol.

14 LIST OF REPORTED TABLES

Tables will be numbered within their section in ascending order. In this SAP the numbering of all TLFs is done according to the ICH guidelines.

Note that TLFs in this SAP may differ slightly from the layout of the IA SAP tables. That is due to the fact that the IA SAP was created according to the old ECRON ACUNOVA standard and the current SAP is written according to the Navitas Life Science standard.

No.	Title	Analysis Set	Corresponding Table in the IA
14.1	**Subject Disposition**	**All Subjects**	
14.1.1	Subject Disposition	Applicable	A 1
14.2	**Demographic Data and Baseline Characteristics**	**SAF, FAS, PPS**	
14.2.1	Demographic Characteristics	Applicable	A 2.1 – A 2.5
14.2.2	Baseline Characteristics - Diagnosis of Qualifying Study Indication	Applicable	Not Applicable
14.3	**Medical History and Concomitant Diseases**	**SAF**	
14.3.1	Relevant Medical History	Applicable	Not Applicable
14.3.2	Concomitant Diseases	Applicable	Not Applicable
14.4	**Previous and Concomitant Medications**	**SAF**	
14.4.1	Prior Medication and Therapies	Applicable	Not Applicable
14.4.2	Concomitant Medication and Therapies	Applicable	Not Applicable
14.5	**Orthopedic surgery**	**SAF**	

No.	Title	Analysis Set	Corresponding Table in the IA
14.5.1	Bone and Tissue Sampling	Applicable	Not Applicable
14.6	**Analysis**	**FAS, PPS**	
14.6.1	**Primary Analysis**	Applicable	
14.6.1.1	Gadolinium Concentration in Trabecular Bone by Renal Function Status	Applicable	A 3.1.1 – A 3.1.5
14.6.1.2	Gadolinium concentration in Cortical Bone by Renal Function Status	Applicable	A 3.1.7 – A 3.1.11
14.6.2	**Secondary Analysis**	**PPS**	
14.6.2.1	Gadolinium concentration in Skin by Renal Function Status	Applicable	A 3.2.1 – A3.2.5
14.6.2.2	Time between last Administration of GBCA and the Date of Tissue Sample Collection	Applicable	Not Applicable
14.6.2.4	Individual eGFR values	Applicable	Not Applicable
14.6.2.5	Potential Co-Factors for NSF and Susceptibility Factors	Applicable	Not Applicable
14.6.2.6	Concomitant Drug Treatments with Potential Impact on Bone Metabolism	Applicable	Not Applicable
14.6.2.7	Concentration of Ca, P, Na, Zn, K and Fe in skin and in tissue of both trabecular and cortical bone determined by ICP-MS	Applicable	Not Applicable
14.6.2.8	Histopathological evaluation of skin samples (taken at time of surgery / surgeries) with regard to the possibility of findings associated with NSF	Applicable	Not Applicable
14.7	**Adverse Events**	**SAF, FAS, PPS**	
14.7.1	Summary of Adverse Events	Applicable	Not Applicable
14.7.2	Adverse Events by System Organ Class and Preferred Term (MedDRA Version x.x)	Applicable	Not Applicable
14.7.3	GBCA Related Adverse Event by System Organ Class and Preferred Term (MedDRA Version x.x)	Applicable	Not Applicable
14.7.4	Serious Adverse Events by System Organ Class and Preferred Term (MedDRA Version x.x)	Applicable	Not Applicable

No.	Title	Analysis Set	Corresponding Table in the IA
14.7.5	GBCA Related Serious Adverse Events by System Organ Class and Preferred Term (MedDRA Version x.x)	Applicable	Not Applicable
14.7.6	Serious Adverse Events and Death by Subject (MedDRA Version x.x)	Applicable	Not Applicable

15 LIST OF REPORTED FIGURES

Not applicable.

16 LIST OF REPORTED SUBJECT DATA LISTINGS

In general, subject data listings should include all subjects with data. The numbering of all TLFs is following the ICH guidelines.

To display all necessary subject data for the IA there was only one subject data listing created. Since this SAP will display all available data for all included subjects, there will be no equivalent listing to the IA SAP. The provided IA listing is a combination out of subject data listing 16.2.2.1, 16.2.6.1 and 16.2.6.2.

No.	Title
16.2.1	**Subject Disposition**
16.2.1.1	Subject Enrolled but Surgery did not take place
16.2.1.2	Subjects who Discontinued Prematurely
16.2.1.3	Subjects Applying for Interim Analysis
16.2.1.4	Protocol Violations
Preface A	List of Inclusion and Exclusion Criteria
16.2.1.5	Eligibility Criteria
16.2.2	**Demographic Data and Baseline Characteristics**
16.2.2.1	Demographic Characteristics
16.2.2.2	Baseline Characteristics - Diagnosis of Qualifying Study Indication
16.2.3	**Medical History and Concomitant Diseases**
16.2.3.1	Relevant Medical History and Concomitant Disease(S)
16.2.4	**Previous and Concomitant Medication**
16.2.4.1	Prior and/or Concomitant Medication and Therapy
16.2.5	**Orthopedic surgery**

No.	Title
16.2.5.1	Bone and tissue sampling by Surgery Number
16.2.6	**Analysis**
16.2.6.1	Gadolinium Contrast Agent (GBCA)
16.2.6.2	Dosing Timepoints and Intervals
16.2.6.3	Vascular, Thrombotic and/or Proinflammatory Events
16.2.6.4	Concomitant Drug Treatments with Potential Impact on Bone Metabolism
16.2.6.5	Serum Concentrations
16.2.6.6	Iron Mobilization Events
16.2.6.7	Disorders Related to T4/Tsh
16.2.6.5	Erythropoietin Treatments
16.2.6.6	Histopathological evaluation of skin samples
16.2.7	**Adverse Events**
Preface B	Legends to Adverse Events
16.2.7.1	Adverse Events
16.2.7.2	Original Onset and End Dates and Times of Adverse Events
16.2.8	**General Checks**
16.2.8	General Checks by Visit
16.2.9	**End of Study**
16.2.9	End of Study

17 MOCKUPS OF TABLES AND SUBJECT DATA LISTINGS

Please note: Yellow resp. cursive texts are working advices.

In General:

- *Required margins: at least 1.0 cm on the upper and lower margin and at least 1.5 cm on the left and right sides. All tables and listings will be landscape and centered format. All figures will be landscape and centered format, unless portrait orientation suggests that the information presented is easier to interpret.*
  All output should have the following header at the upper left margin:
  <Sponsor>
  Protocol No.: <Protocol No.>
  and the following header at the upper right margin:
  <Draft/Final Version>, ddmmmyyyy
  Page n of N
- *Tables/appendices/listings should be internally paginated (i.e., page numbers should appear sequentially within each table). The name of the SAS program used to generate the output shall be displayed in the lower left corner. SAS Monospace, font size 8 will be used, although the mockup below would indicate differently.*
- *Tables of Contents will be generated separately for Tables and Listings, listing numbers and titles. A file separate from Tables and Listings output must be produced. TOC pages will bear the standard header.*

Tables in general:

- *Each table will present all types of renal function in separate columns and next to each other. If necessary, add a column for total.*
- *If applicable tables will be repeated by treatment (Control, GBCA-Overall, Gadobutrol, Gadodiamide, Gadopentetic acid, Gadoteric acid, Gadoversetamide, and Gadoxetic acid) and by treatment and dose (single/multiple) separately.*

Data Listings in general:

- *All Listings should be - paged by treatment and sorted by renal function, subject and actual date and time.*

Use the appropriate table type as shown below. For more detail description refer to NLS Catalog for Mock ups to support the SAP.

17.1 Tables

Navitas Life Sciences GmbH
Protocol No.: ALS-Gd64/001 Version 4.0

Date: ddmmmyyyy
Page n of N

Table of Contents

Table Number	Title	Analysis Set
Table 14.1	Subject Disposition	All Subjects
...		
...		

Please, provide as separate file

YYYYY.sas SAS Version: XX

Type 1: Frequencies

Navitas Life Sciences GmbH
Protocol No.: ALS-Gd64/001 Version 4.0

Date: ddmmmyyyy
Page n of N

Table 14.x.x
Title

Analysis Set: SAF, FAS, PPS, *Treatment ∏ Single Dose*

Characteristic	*Total (N=xxx)*	Stable Normal Renal Function (eGFR > 60 ml/min/1.73 m2) (N=xxx)	At least Moderate Impaired Renal Function (eGFR <= 60 ml/min/1.73 m2) (N=xxx)	*Missing Renal Function*
Variable 1 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Category 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sub-Category 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sub-Category 2	...	...	...	...
Sub-Category 3	...	...	...	...
	...	...	...	...
Category 2	...	...	...	...
Sub-Category 4	...	...	...	...
Sub-Category 5	...	...	...	...
	...	...	...	...
Variable 2 n (%)	...	...	...	...
Category 1	...	...	...	...
Sub-Category 1	...	...	...	...
...	...	...	...	...

Footnotes
Use Treatment, Dose Category and Sub-Category only if necessary. For each population start a new page. If necessary, add footnotes.

YYYYY.sas SAS Version: XX

Sponsor Name: Navitas Life Sciences GmbH
Statistical Analysis Plan (SAP)
Version No.: Final 1 Date: 31JUL2019

Short Title of Study: Long-Term Retention of Gadolinium in Bone
Sponsor Study No.: ALS-Gd64/001
NLS Study No.: 665

Type 2: Summary Statistics

Navitas Life Sciences GmbH
Protocol No.: ALS-Gd64/001 Version 4.0

Date: ddmmmyyyy
Page n of N

Table 14.x.x
Title

Analysis Set: *SAF, FAS, PPS Treatment - Single Dose*

Characteristic	*Total*	Stable Normal Renal Function (eGFR > 60 ml/min/1.73 m2)	At least Moderate Impaired Renal Function (eGFR <= 60 ml/min/1.73 m2)	Missing Renal Function
Variable 1				
Category 1				
Sub-Category 1				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
...	...	...	...	...
Sub-Category 2				
...				
Variable 2				
Category 1				
n				
...				

Footnotes

Use Treatment, Dose, Category and Sub-Category only if necessary. Provide all statistics according to 8.1. For each population start a new page. If necessary, add footnotes.

YYYYY.sas SAS Version: XX

Sponsor Name: Navitas Life Sciences GmbH
Statistical Analysis Plan (SAP)
Version No.: Final 1 Date: 31JUL2019

Short Title of Study: Long-Term Retention of Gadolinium in Bone
Sponsor Study No.: ALS-Gd64/001
NLS Study No.: 665

Type 3: Frequencies and Summary Statistics Combined

Navitas Life Sciences GmbH
Protocol No.: ALS-Gd64/001 Version 4.0

Date: ddmmmyyyy
Page n of N

Table 14.x.x
Title

Analysis Set: *SAF, FAS, PPS Treatment*

Characteristic	*Total*	Stable Normal Renal Function (eGFR > 60 ml/min/1.73 m2)	At least Moderate Impaired Renal Function (eGFR <= 60 ml/min/1.73 m2)	Missing Renal Function
Variable 1 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Category 1	...	...	...	...
Sub-Category 1	...	...	...	...
Sub-Category 2	...	...	...	...
Sub-Category 3	...	...	...	...
Category 2	...	...	...	...
Sub-Category 4	...	...	...	...
Sub-Category 5	...	...	...	...
Variable 2				
Category 3				
Sub-Category 1				
n	...	...	...	...
Mean	...	...	...	...
SD	...	...	...	...
...				

Footnotes

Use Treatment, Category and Sub-Category only if necessary. Provide all statistics according to 8.1. For each population start a new page. If necessary, add footnotes.

YYYYY.sas SAS Version: XX

17.2 Subject Data Listings

All variables out of all available case report forms (CRFs) will be listed. Each subject data listing will be paged by treatment and renal function will be the first column followed by Subject ID. The Subject Data Listing which is presented below after table of contents is only an example, it will be expended according to study objectives and CRF.

```
Navitas Life Sciences GmbH                                                    Date: ddmmmyyyy
Protocol No.: ALS-Gd64/001 Version 4.0                                           Page n of N
                                        Table of Contents

 Listing Number          Title
 ---------------------------------------------------------------------------------------------

 16.2.1.1                ...


 ...                     ...

 ---------------------------------------------------------------------------------------------
```

Please, provide as separate file.

```
YYYYY.sas    SAS Version: XX
```

Navitas Life Sciences GmbH
Protocol No.: ALS-Gd64/001 Version 4.0

Date: ddmmmyyyy
Page n of N

Subject Data Listing 16.2.x.x
Title

Treatment: xxxxx

Renal Function	Subject ID	...	...	...	...	...	...	...	...	...	...	...
xxxx	xxxx	...	...	...	...	...	...	...	...	...	...	...
	xxxx	...	...	...	...	...	...	...	...	...	...	...
xxxxxx	xxxx	...	...	...	...	...	...	...	...	...	...	...
	xxxx	...	...	...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...	...	...	...	...

YYYYY.sas SAS Version: XX