STATISTICAL ANALYSIS PLAN

CLA-17-01 - GBCA Study

A study of pattern of use for gadolinium-based contrast agents (GBCAs) in patients undergoing contrast-enhanced magnetic resonance (CE-MR) examination

A cross-sectional, multicentre, observational study with prospective data collection

Version 1.0: 22-JAN-2019

SIGNATURES

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
BMI	Body mass index
CE	Contrast enhanced
CSP	Population by country/site
CT	Computed tomography
eGFR	Estimated glomerular filtration rate
EMA	European Medicine Agency
FEP	Full eligible population
FIP	Full included population
GBCA	Gadolinium-based contrast agents
GBCAP	Population by GBCA type
GFRP	Population by GFR rate
HISALP	Population by history of allergy
MR	Magnetic resonance
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PET	Positron-emission tomography
PT	Preferred Term
SAF	Safety population
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
SPECT	Single photon emission computed tomography
SPP	Population by specialty

1 INTRODUCTION

1.1 Rationale for study

It is currently unknown and of high scientific interest with which dosages the radiologists use the gadolinium-containing contrast media currently available in their market. Such information, which is very important for the referring physicians, can only be obtained by up-to-date observation and documentation in the daily routine.

It is also currently unknown and of further interest for the assessment of the applications, which criteria referrers consider for the administration of gadolinium-containing contrast agents after the publication of the EMA/457616/2017 requirements. In particular, it is unknown whether the presence of pre-existing renal insufficiency is taken into consideration, how often MR contrast agents are used in the same patient and whether this is dependent on indication and/or comorbidities. For example, this question is relevant to patients evaluated for multiple sclerosis and cancers, where it is unknown if notwithstanding the known brain retention of gadolinium, repeated contrast enhanced MR scans are considered necessary. Also, it is unknown if dose reductions, perhaps dependent on scanner magnetic field strength, are applied.

The study plan/protocol and the resulting documentation sheet of the requested study accurately collects data useful to clarify these points and will therefore provide more accurate insight into the potentially adapted clinical procedure.

1.2 Purpose of the analyses

The study is set-up for descriptive purposes, no a priori hypothesis will be tested.

The statistical analysis plan (SAP) is a more detailed description of the statistical rationale and the methods used for generating the results of this observational study.

It contains additional information not covered by the study protocol (Version 1.5, 28-Nov-2018).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

Primary objectives:

The primary objective of the GBCA observational study, will be to prospectively collect data on the pattern of use for GBCA in real-life setting with special reference to Clariscan after its commercial launch in Europe.

Secondary objectives:

The study will look at the effectiveness and safety profile of GBCAs including Clariscan in clinical practice

3 STUDY METHODS

3.1 Study design and plan description

This is a prospective, multi-center observational study.

It is planned to enroll up to 5400 patients from 7 countries and 14 sites.

3.2 Study variables

3.2.1 Patient data

3.2.1.1 Signed informed consent

- Yes/Date
- No

3.2.1.2 Demographics and baseline characteristics

- Age
    - Child: birth – 4 weeks, 5 weeks – 6 month, 7 month – 12 month. 13 month – 2 years, 3 years – 4 years, 5 years - 9 years, 10 years to 18 years; Adult: 19 Years to 89 years, > 89 years; for adults aged 19-89 years the exact age will be documented)
    - Pediatric:0-18 years, non-elderly adults: 19 to 59 years, elderly adults: ≥60 years

- Gender (male/female)
- Pregnancy status (yes, no, not applicable)
    - If applicable weeks of pregnancy (on day of visit)
- Weight (kg)
- Height (m)
- BMI will be derived from weight and height via BMI=weight (kg)/height(m)^2

3.2.1.3 Medical summary

- Diagnosis to which MR scan has been indicated
- Question to be answered with the use of CE-MR
- Secondary diagnosis
- Reason for using a contrast medium (border delineation of pathology, overall morphological characterization of pathology/lesion, overall increase in resolution of images required, confirmation of opinion/diagnosis, for comparison with non-contrast enhanced images, angiography or myocardial assessment, standard procedure for this diagnostic question, other)
- Specific reason why the GBCA was used
- Comorbidities (none, allergy, diabetes mellitus, heart failure, hepatic impairment, hypertension, neurologic symptom, renal impairment, autoimmune disease, malignancy/cancer, other)
    - Allergy status for patients with allergies (bronchial asthma, eczema, food allergy, urticaria, previous history of allergy to other contrast media [unknown media, Iodine-based media, Gadolinum-based media, ultrasound media, other media)
    - Renal status eGFR for patients with renal impairment (< 15, 15-30, 31-60, > 60 mL/min/m^2, impaired [exact eGFR unknown], unimpaired [exact eGFR n/a])
        - If renal status < 60 mL/min/m^2: status of renal replacement for the compromised kidney(s) (renal replacement – dialysis, renal transplant, no replacement)
- Pre-medications (none, steroids, anti-histamines, other)
- Concomitant medications (no co-medication, chemotherapy/active treatment for malignancy, radiotherapy, anti-hypertensives, diabetic medications, heart failure treatment, nephrotoxic medication [antibiotics, iodinated agents, oncological drugs, immunosuppressants, other], other)
- Source of funding for the scan (self-funded [n/a, full, partially], paid by personal/hospital insurance, reimbursed by the state)

- If funding = insurance or reimbursed, what is being paid for (contrast media, procedure, procedure including contrast media)

3.2.1.4 Referral details

- Quality of referral notes (not enough information, satisfactory levels of information, detailed information with clear medication)
- Referral type (routine, emergency, follow-up, repeat scan identical to previous scan)
    - If repeat scan, reason for repeat scan (poor quality image [patient-related factors, contrast-related factors, imaging-technique related factors], other)
- Referring physician seniority (resident, registrar or equivalent; consultant or equivalent; consultant with a specialist interest in the field)
- Referring physician specialty (cardiology, gastroenterology, gynecology, internal medicine, neurology, oncology, orthopedics, respiratory medicine, rheumatology, urology, other)

3.2.1.5 MR Examination

- Organ/system under examination (brain/meninges/spinal cord, head and neck, breast, bronchial tissue/lungs, cardiovascular, renal, hepatobiliary, pancreas, gastrointestinal tract, urinary tract incl. bladder, genital tract incl. gonads, endocrine glands, muscoskeletal system incl. bones/joints/muscles, lymphoid tissue incl. blood disorders, whole body, other)
- Indication (CNS indication [brain/meninges/spinal cord], organ/whole body [all other organs (if not MRA like a cardiovascular MRA)], angiography [any MRA])
- MRI details (if applicable)
    - Brand of contrast agent
    - Volume of contrast agent (ml)
    - Injector use (yes/no)
    - Volume of saline follow-up injection (none or in mL)
    - Scanner make (GE, Siemens, Philips, other)
    - Field strength (1.5T, 3T, >3T)
    - Scanner model
    - Scan modality (dynamic, delayed, both dynamic and delayed)

    - Type of sequence/protocol (standard, modified)
        - If modified, reason for modifying the sequence (improvement of image quality, removal of artifacts preventing a diagnostic image, patient related reason, other)

- MRA details (if applicable)
    - Brand of contrast agent
    - Volume of contrast agent (ml)
    - Injector use (yes/no)
    - Volume of saline follow-up injection (none or in mL)
    - Scanner make (GE, Siemens, Philips, other)
    - Field strength (1.5T, 3T, >3T)
    - Scanner model
    - Scan modality (dynamic, delayed, both dynamic and delayed)
    - Type of sequence/protocol (standard, modified)
        - If modified, reason for modifying the sequence (improvement of image quality, removal of artifacts preventing a diagnostic image, patient related reason, other)
- MRA or MRI part of a broader pathway to clarify the illness under investigation (yes, no)
- Any other image scan before the MR scan in relation to the illness under investigation (none, CT, ultrasound, CE-MR, liver-specific MR, non-CE-MR, SPECT, PET, X-ray (excluding CT), other)

3.2.1.6 Diagnosis after MRI

- Did contrast enhanced MRI change radiological diagnosis (yes, no)
- Did contrast enhanced MRI increase the radiologist's confidence in diagnosis compared to non-contrast enhanced MRI (yes, no)
- Radiologist's confidence in diagnosis at the time of referral, before CE-MRI (visual analogue scale 0-100%)
- Radiologist's confidence in diagnosis at the time of referral, after CE-MRI (visual analogue scale 0-100%)
- Quality of CE-MRI image (poor/inadequate, fair/partial, good/adequate, excellent)

3.2.1.7 Diagnosis after MRA

- Did contrast enhanced MRA change radiological diagnosis (yes, no)
- Did contrast enhanced MRA increase the radiologist's confidence in diagnosis compared to non-contrast enhanced MRA (yes, no)
- Radiologist's confidence in diagnosis at the time of referral, before CE-MRA (visual analogue scale 0-100%)
- Radiologist's confidence in diagnosis at the time of referral, after CE-MRA (visual analogue scale 0-100%)
- Quality of CE-MRI image (poor quality & blurred arterial segment, fair/inadequate for confident diagnosis, good/adequate for confident diagnosis, excellent/adequate for highly confident diagnosis)

3.2.1.8 Adverse Events

- Adverse Event (AE) verbatim
- Serious AE (yes, no)
- Date/time of onset
- Date time of ending
- Causality (not related, possibly related, probably related, definitely related)
- Onset of AE (immediate [up to 1-hour post-injection], delayed [between 1 h and 7 days post-injection]
- Severity of AE (mild/tolerable, moderate/interferes with normal activity, severe/incapacitating)

3.2.2 Investigator data

- Date of first patient
- Date of last patient
- Total number of patients visited by this investigator during the study period
- Number of procedures performed by the investigator (liver-specific MR, Non-CE MR, CE-MRI, CE-MRA, CT, ultrasound, PET-PET/CT-PET/MR, SPECT, X-ray, other)

3.2.3 Centre data

- Number of available scanners in centre (MRI, CT, ultrasound, PET-PET/CT, PET/MR, SPECT, X-ray)
- Number of procedures performed in the centre (liver-specific MR, Non_CE MR, CE-MRI, CE-MRA, CT, ultrasound, PET-PET/CT-PET/MR, SPECT, X-ray, other) during the study period
- Number of staff members (radiologists, radiographers, nurses)
- Decision for use of a specific contrast medium (individual decision, collective decision)
- Decision maker for use of specific contrast medium (Head of radiology department, radiologist, specialty physician, pharmacist, manager [non-clinician], other)
- Challenges faced by radiology department
- User satisfaction with GBCA packaging and injectors
    - for each GBCA
        - Satisfaction with GBCA packaging (could be improved, o.k., excellent/particularly good)
        - Satisfaction with injector (could be improved, o.k., excellent/particularly good)

4 SAMPLE SIZE CALCULATION

The sample size is not based on statistical considerations, as the study does not formally test a hypothesis.

5 GENERAL STATISTICAL CONSIDERATIONS

5.1 General principles

Analysis will be performed using SAS software package release Version 9.4.

5.2 Timing of analyses

An interim analysis of the data sampled until mid of February 2019 is planned.

5.3 Covariates and subgroups

Endpoints will additionally be stratified by site, specialty, country, GBCA type, scanner type, scanner field strength, scan modality where applicable

5.4 Handling of dropouts

Not applicable

5.5 Handling of missing data

All analyses will be performed without replacing missing values.

5.6 Multi-center studies

Not applicable

5.7 Multiple testing

Due to the explorative design of the observational study there will be no adjustments for multiple statistical tests.

5.8 Statistical significance (p-values)

A p-value of <0.05 will be declared as statistically significant.

6 ANALYSIS SETS

The allocation of subjects to analysis sets will be determined by the sponsor and the CRO on a per-subject basis immediately before data base lock.

Full eligible population (FEP)

The FEP population consists of all screened subjects, both successful and failed screens.

Full included population (FIP)

The FIP population consists of all successful screens.

Safety population (SAF)

The SAF population consists of all patients with a documented MRI/MRA procedure.

Population by country/site (CSP)

The CSP population consists of all successful screens in with known country/site.

Population by GBCA type (GBCAP)

The GBCA population consists of all subjects with known GBCA brand type.

Population by speciality (SPP)

The SPP population consists of all subjects examined for an ailment with known speciality.

Population by GFR rate (GFRP)

The GFR population consists of all subjects with known range of GFR rate.

Population by History of allergy (HISALP)

The history of allergy population consists of all subjects with known history of allergy status.

7 STATISTICAL METHODS

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, minimum and maximum. The frequency and percentages (based on the non-missing sample size) will be reported for categorical measures. Data that will be listed will be sorted by country, site and subject.

For the comparison of endpoints in stratified analyses (e.g. by country, by GBCA etc.) explorative statistical tests will be applied (ANOVA for continuous endpoints, Chi-Square tests for categorical endpoints) if feasible.

7.1 Subject data

7.1.1 Subject disposition

- Number of subjects screened
- Number of screening failures

This will be shown by analysis population for all subjects (FIP), by site (CSP) and by specialty (SPP).

- Observation period in days
    - Observation period will be derived from the end of study questionnaire as observation period = Date of last patient – date of first patient +1
- Total number of patients in the observation period
- Actual number patients in the observation period (absolute and percentage of total number of patients)

This will be shown by analysis population for all investigators (FIP) and by site (SPP).

7.1.2 Demographics and other baseline characteristics

Demographics and baseline characteristics will be analysed descriptively for all patients (FIP), by GBCA (GBCAP) and by site (SPP).

7.1.3 Diagnosis and reason for contrast media

The number and frequency of diagnoses (primary and secondary), diagnosis questions, main reason and specific reason for using contrast media will be analysed for all patients (FIP), by site (SPP) and by specialty (SPP). Additionally, the main reason for using contrast media will be shown by GBCA (GBCAP).

The precision of the diagnostic criteria (derived from the diagnostic text field on a scale from 0-3, 0=extremely vague, 1=approximate, 2=sufficiently defined, 3=very defined) and the categories of the diagnostic question (rule-in *vs* rule-out *vs* diagnosis refinement *vs* diagnosis clarification) will be analysed for all patients (FIP), by site (SPP), by specialty (SPP) and by GBCA (GBCAP). Precision of diagnosis will be an derived from existing data and will be performed by GEHC

7.1.4 Medical history

The number and frequency of comorbidities, pre-medications, concomitant medications and patients with previous scans will be analysed for all patients (FIP) and by GBCA (GBCAP). Additionally, number and frequency of previous scans will be shown by site (SPP) and by country (CSP). For patients with allergies, further details about the allergy status will be tabulated. For patients with renal impairment eGFR and the renal replacement status will be analysed.

A patient is defined to have a previous scan if either the referral type is a repeat scan or any other image scan has been performed before the contrast enhanced MR scan session in relation to the illness under investigation.

7.1.5 Funding

The number and frequency of the source of funding, full or partially self funding and what is being paid for will be analysed for all patients (FIP), by country (CSP), by specialty (SPP) and by GBCA (GBCAP).

Additionally type of funding will be stratified by quality of referral.

7.1.6 Referral

The number and frequency of the quality of referral notes, quality stratified by type of referral, quality of referral notes stratified by seniority, type of referral, seniority, specialty, repeat scans, reason for repeat scans and reason for repeat scans stratified by type of referral will be analysed for all patients (FIP), by site (CSP), and by country (CSP).

Repeat scans, reason for repeat scans and reason for repeat scans stratified by type of referral will additionally be analysed for all patients (FIP), by site (CSP), by country (CSP), by specialty (SPP) and by GBCA type (GBCAP).

7.1.7 Injection and scanning

The volume of contrast agent, the volume of saline follow-up injection and the dose, the number and frequency of injector usage, the sequence type (standard vs modified, coded specific sequence type), the reason for modified sequence will be analysed for all patients (FIP), by site (CSP), by country (CSP), by specialty (SPP), by GBCA (GBCAP), by scanner type (FIP), by scanner field strength (FIP) and by scan modality (MRA/MRI).

The sequence type will additionally be analysed by injection protocol for all patients (FIP), by site (CSP), by weight (FIP) and by country (CSP).

The mean volume of contrast agent and the volume of saline follow-up injection will be shown in a bar chart for type of sequence.

The dose in mmol/kg will be calculated according to

Dose = injected volume * GBCA concentration / weight

Where GBCA concentration = 1 mmol/mL for Gadovist and

0.5 mmol/mL for all other GBCA

Dose will also be analyed for the following categorisation:

≤0.1, > 0.1 to 0.2, > 0.2 to 0.3 and >0.3 mmol/kg

for all patients (FIP), by GBCA (GBCAP), by age groups (FIP), by GFR rate (GFRP), and by indication (see 3.2.1.5).

7.1.8 Diagnostic impact

The number and frequency of the changes of radiological diagnosis, the increase in confidence of the diagnosis and the quality of the image, the confidence in diagnosis at the time of referral before and after CE/MRI(MRA), quality of the image stratified by age, country (CSP), site (CSP) and by GBCA (GBCAP), type of referral, quality of referral notes stratified by seniority, type of referral, seniority, specialty, repeat scans, reason for repeat scans and reason for repeat scans stratified by type of referral will be analysed for all patients (FIP), by site (CSP), by specialty (SPP) and by GBCA (GBCAP).

In addition, the change in radiological diagnosis and the change in increase of confidence will be will be shown in a bar chart for the different categories of quality of referral notes.

The quality of the image will be shown in a bar chart for the different categories of the change in radiological diagnosis and the confidence in diagnosis.

7.2 Centre data

7.2.1 Staffing and equipment

The overall number of staff members (radiologists, radiographers, nurses) as well as the different type of staff, the overall number of scanners and the type of scanners, the number of procedures during the study period, the type of decision and the decision makers, and the challenges will be analysed for all sites and by country.

7.2.2 User satisfaction

Packaging satisfaction, injector satisfaction will be analysed overall, by country and by GBCA. In addition, the reason for ratings will be given for the different satisfaction categories. These will be ordered by frequency.

7.3 Adverse events

Analysis of safety will be based on the safety population (SAF).

The number and frequency of patients with adverse events and serious adverse events will be analysed overall, by age group (SAF), by history of allergy (HISALP), by GFR rate (GFRP), by site (CSP) by country (CSP), by specialty (SPP) and by GBCA (GBCAP) by MedDRA SOC and PT.

The number and frequency of adverse events will also be analysed for the subgroups given above stratified by causality, treatment, severity and onset of the adverse event.

8 TABLES AND LISTINGS

Tables, figure and listings generated for this study are listed in Appendix 1.

9 REPORTING CONVENTIONS

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics, will be reported to one decimal place greater than the original data. Median, or minimum and maximum will use the same number of decimal places as the original data.

10 DOCUMENT HISTORY AND CHANGES IN THE PLANNED STATISTICAL ANALYSIS

Version No.	Date	Author	Sections changed	Brief description of change
1.0	22-JAN-2019	U. Elsasser	n/a	First version

APPENDIX 1: LIST OF TABLES/FIGURES/LISTINGS