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STATISTICAL ANALYSIS PLAN No GDX-44-008

PROOF OF CONCEPT STUDY CONCERNING EFFICACY OF P03277 MR IMAGING IN HCC DIAGNOSIS

Phase IIa clinical study

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BIOSTATISTICIAN [redacted]	**Date and Visa**
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HISTORY FORM

Version	Date	Reason for change
1.0	03 DEC 18	First release
2.0	11 JUN 19	[redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AFP	Alpha fetoprotein
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
ATC	Anatomical Therapeutic Chemical Drug dictionary
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
BW	Body Weight
CNR	Contrast to Noise Ratio
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
DRM	Data Review Meeting
EASL	European Association for the Study of the Liver
eGFR	estimated Glomerular Filtration Rate
EORTC	European Organisation for Research and Treatment of Cancer
FAS	Full Analysis Set
GRE	Gradient echo sequences
HBV	Hepatitis B
HCC	Hepatocellular carcinoma
HCV	Hepatitis C
IMP	Investigational Medicinal Product
IV	Intravenous
LDH	Lactate DeHydrogenase
MCV	Mean red blood Cells Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NASH	Non-alcoholic steato hepatitis
PE	Percentage Enhancement
PPS	Per Protocol Set
PT	Preferred Term
RBC	Red Blood Cells
ROI	Region Of Interest
SAE	Serious Adverse Event
SD	Standard Deviation
SI	Signal Intensity
SNR	Signal to Noise Ratio
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
WBC	White Blood Cells

TABLE OF CONTENTS

1. SUMMARY OF THE STUDY PROTOCOL

This document presents the statistical analysis plan (SAP) for Guerbet, Protocol No. GDX-44-008: "Proof of Concept study concerning efficacy of P03277 MR Imaging in HCC diagnosis".

This analysis plan is based on the final protocol Version 4.0 including amendment n°2 dated December 12th, 2017.

1.1. Study objectives

The primary objective is to evaluate the diagnostic value (specificity and sensitivity) for hepatocellular carcinoma (HCC) of P03277 MR Imaging in patients with suspected small nodules and chronic liver disease.

The secondary objectives of the study are to evaluate multiple quantitative and qualitative efficacy parameters and the safety (clinical and biological) profile of P03277 following single administration in patients with suspected HCC.

1.2. Study design

GDX-44-008 is a Phase IIa, dual center, exploratory, non-randomized, open label, two cohorts, two doses study.

After a patient has satisfied all eligibility requirements, he will undergo 4 visits:

- Visit 1: screening (D-7 to D0). The maximum period between patient's screening and administration of P03277 is 7 days but can be the same day if eGFR measurement within the last 7 days is available.
- Visit 2: inclusion/dosing/MRI and post-injection follow-up (D0). Patient inclusion will be confirmed on the day of administration of P03277 according to the eGFR results and urinary pregnancy test if applicable
- Visit 3: safety visit (D+1 post injection).
- Visit 4: Optionally and according to local standard of care for histology analysis, the patient will have a specific biopsy or a surgically resected specimen collected at the time of loco-regional treatment. This procedure, whatever the type (biopsy or surgery), should be done between 3 days after P03277 administration and 13 weeks maximum. Alternatively it is acceptable to record results from histology done within 2 months prior to P03277 administration.

The standard of reference for diagnosis will be given by the site according to their standard of care and adapted from EASL/EORTC diagnostic criteria and considering previous contrast enhanced imaging (CT and/or MRI) and/or biopsy specimen analysis given on-site and/or the more recent AFP results available.

The duration of patient's participation could be from 2 days up to 3 months approximately. The study will be considered as completed once all the images collected for all the patients will have been reviewed by expert readers.

The images will be assessed for the primary criterion by 2 expert readers. For secondary criteria, they will also be assessed on-site by a radiologist expert in liver diseases and/or by the 2 expert readers. In case of diagnostic discordance for the primary criterion, a consensus meeting will be organized after nodule comparison. In this case the qualitative evaluations will be reviewed globally and may be modified.

Safety assessments will be based on adverse events, injection site tolerance, clinical laboratory parameters and vital signs.

The primary endpoint in this study is the nodule diagnosis with P03277 imaging compared to the nodule diagnosis obtained with the standard of reference.

P03277 will be injected at a dose of 0.1 mmol/kg BW for cohort 1 (corresponding to 0.2 mL/kg BW) and 0.05 mmol/kg BW for cohort 2 (corresponding to 0.1 mL/kg BW) via a peripheral vein (the antecubital vein is preferred).
P03277 will be administered by intravenous (IV) bolus injection at 2 mL/s rate without dilution, followed by a 0.9% saline flush at same rate to ensure complete injection of the contrast medium.
The P03277 administration is to be performed by power injector in order to better control injection rate.

2. EVALUATION CRITERIA

2.1. Demographic and other baseline characteristics

Demographic data are: sex, age, childbearing potential, body weight, height, body mass index, race and ethnic origin.

BMI will be derived when weight and height are available using the formula:

$$BMI = \frac{Body\ Weight\ (kg)}{Height\ (m)^2}$$

Baseline characteristics are:

- patient's history (including the medical history, intolerance history)
- physical examination
- chronic liver disease status at inclusion: documentation supporting the diagnosis of chronic liver disease (biopsy, endoscopic, biological, ultrasound parameters, and elastography), aetiology of chronic liver disease (alcohol, HBV, HCV, non-alcoholic-NASH, other specify) and last evaluation of Child-Pugh score available (including the date)
- documentation of modality for detection of suspected nodules and date
- concomitant treatments on-going at the time of screening/inclusion and ended before administration of P03277
- blood samples collection at screening or inclusion visit

The laboratory data analysis will be performed by the site laboratory.
The following parameters will be assessed:

- Hematology: red blood cells (RBCs), hemoglobin, hematocrit, Mean red blood Cells Volume (MCV), white blood cells (WBCs), neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet count.
- Biochemistry: sodium, potassium, chloride, calcium, phosphate, glucose, total protein, creatinine, eGFR, blood urea nitrogen (BUN) / urea, cystatin C, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, total bilirubin, conjugated and unconjugated bilirubin, triglycerides (TG), lactate dehydrogenase (LDH).
  - eGFR evaluated locally for screening purpose.

2.2. Efficacy criteria

Efficacy variables are derived from the reader's evaluations of the imaging examination. All images will be read either by two readers, in which case a consensus will be done for any discrepancies on diagnosis between the two readings, or on-site by only one assessor. An overview of the efficacy variables is provided in the following table:

Variables	On-Site Reading	Expert Reading
Primary efficacy variables		
Nodule diagnosis		✓
Secondary efficacy variables		
Technical adequacy of images	✓	✓

Number of nodules evaluated	✓	✓
Imaging qualitative evaluation (nodule intensity, presence of intranodule iron and fat and visualization of perilesional capsule)		✓
Visualization of biliary and liver vascular abnormalities		✓
Very delayed imaging qualitative evaluation for parenchyma enhancement and nodule signal enhancement relative to parenchyma		✓
Quantitative evaluation of nodule intensity and vascular intensity: SI measurements in nodules, liver, background, aorta and the portal vein for SNR CNR PE	✓	

2.2.1. Primary criterion

The primary criterion of the study is the nodule diagnosis with P03277 imaging (HCC, not HCC). It will be assessed:

- On a maximum of 3 hepatic nodules per patient
- Based on visual qualitative analysis of P03277 triphasic imaging (arterial, portal and delayed phases) showing HCC typical hallmarks according to EASL/EORTC criteria (arterial hypervascularization and portal wash-out or delayed wash-out)
- By two experts readers. In case of discordance, a consensus diagnosis will be obtained.

The standard of reference for diagnosing liver nodules (HCC, other malignant, regenerative or dysplastic nodule, benign, uncertain) will be given by the site according to their standard of care and according to adapted EASL/EORTC diagnostic criteria, considering previous contrast enhanced imaging (CT and/or MRI) and/or histology analysis and/or the more recent AFP results available.

HCC will be considered:

- With P03277 when experts reading/consensus consider the nodule as being HCC
- With standard of reference when:
  - Diagnosis of any biopsy is HCC
  - Diagnosis of the history imaging is HCC

Suspected nodule characterization, mapping and measurement of previous contrast enhanced imaging will be described. Previous alpha-fetoprotein value will be presented.
Nodule characterization from histopathology will be presented.
Results (HCC, not HCC) of nodule examinations used for standard of reference from histopathology or previous imaging will be presented.

2.2.2. Secondary efficacy criteria

Secondary criteria to support the primary endpoint are the following:

- Technical adequacy of images (on-site and expert reading) assessed as adequate, yes or no and reason for inadequacy will be recorded using a 5 items:
  - 1 = Artifacts due to subject
  - 2 = Artifacts due to machine
  - 3 = Artifacts due to contrast agent

- 4 = Injection technical failure
- 5 = Other, specify

- Visualization of biliary and liver vascular abnormalities (expert reading):
  - presence of portal thrombosis
  - hepatic venous thrombosis
  - biliary tract invasion
  - visualization of arterio-portal fistula within vascular territory of suspected nodule(s)
- Number of nodules evaluated (on-site and expert reading)
  - Number of nodules suspected on-site by P03277 imaging corresponds to sum of nodules at the previous imaging (if same suspected nodules with no difference in segment and site) or sum of nodules reported in the mapping of P03277 imaging.
  - Total number of nodules suspected by experts reading
- Localization and size of suspected nodules (on-site and expert reading)
  - Localization and size of suspected nodules on-site correspond to report at the previous imaging in case of same nodule(s) suspected or from mapping of P03277 imaging
- Imaging qualitative evaluation of nodule intensity and nodule description (expert reading)
  - At each phase (T2, T1 unenhanced, arterial, portal, delayed): nodule (maximum of 3) intensity relative to parenchyma according to the scale:
    - Hypointense
    - Hyperintense (and relative to spleen on T2 if hyperintense)
    - Isointense

    In addition nodules will be described as homogeneous or heterogeneous.
  - Presence of fat and iron within the liver nodules at unenhanced phase in and opposed phase (intra nodule)
  - Visualization of a perilesional capsule (yes/no) at portal phase or delayed phases
  - Wash-out? (Portal and delayed phases)
- Imaging quantitative evaluation of nodule intensity and vascular intensity (on-site reading)
  - At each phase (T1 unenhanced, arterial, portal, delayed, 15 ±5 minutes) SI measurement on nodule (maximum of 3), liver, and background for SNR, CNR, and nodule percentage enhancement (PE):
    - Nodule SNR (Signal to noise ratio) will be calculated at each phase using the following formula: SI_{nodule}/SD_{noise} where SI nodule is "nodule ROI intensity" and SD_{noise} is "Background ROI: SD intensity".
    - Nodule CNR (contrast to noise ratio) will be calculated at each phase using the following formula: $(SI_{nodule} - SI_{liver})/SD_{noise}$ where SI_{nodule} is "nodule ROI intensity"; SI_{liver} is "liver parenchyma ROI intensity" and SD_{noise} is "Background ROI: SD intensity".
    - PE (Nodule Percentage enhancement) will be calculated using the following formula: $(SI_{post} - SI_{pre})/SI_{pre} * 100$ where SI_{post} is the nodule signal intensity at each phase (arterial, portal, delayed, 15 ±5 minutes) and SI_{pre} is the nodule signal intensity at unenhanced sequence.
  - On arterial and on portal phase, SI measurement of the aorta and the portal vein maximum vessel enhancement for SNR calculation purpose
    - Vascular SNR (Signal to noise ratio) will be calculated using the following formula: SI_{aorta}/SD_{noise} where SI_{aorta} is "aorta ROI intensity" and SD_{noise}

is "Background ROI: SD intensity" at arterial phase, $SI_{portal\ vein}/SD_{noise}$ where $SI_{portal\ vein}$ is "portal vein ROI intensity" and SD_{noise} is "Background ROI: SD intensity" at portal and delayed (3 minutes, 15 ±5 minutes) phases. In case of several nodules, mean of SD of background will be used.

- Very delayed imaging qualitative evaluation (expert reading) (15 ±5 minutes, 1h, 2h) for visualization of the parenchyma enhancement relative to unenhanced fat-suppressed GRE T1 sequence (hyperintense, isointense, hypointense) and nodule enhancement relative to parenchyma.

2.3. Safety criteria

2.3.1. Adverse events

Adverse Events (AEs) will be recorded throughout the patient participation until 1 day after injection of P03277. Only AEs that the investigator considers as related to P03277 and/or the study procedures will be recorded at the optional visit 4 between 3 days and 3 months after P03277 administration.

2.3.2. Tolerance at injection site

For all patients, injection site tolerance (burning, pain, eruption, extravasation, inflammation or other) will be assessed over 1 day following the contrast agent injection (during the injection up to 30 ± 5 minutes and the day after injection) and over a longer period if the investigator becomes aware of any related AE. In case of injection site pain, the patient will be asked to specify the level of pain using a visual analogic scale (VAS) from 0 (no pain) to 10 (maximal pain).

2.3.3. Clinical laboratory parameters

For each patient, blood samples will be performed at Day+1. A central laboratory will be used to analyse and report blood chemistry/haematology.
The following parameters will be assessed:

- Hematology: red blood cells (RBCs), hemoglobin, hematocrit, Mean red blood Cells Volume (MCV), white blood cells (WBCs), neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet count.
- Biochemistry: sodium, potassium, chloride, calcium, phosphate, glucose, total protein, creatinine, eGFR, blood urea nitrogen (BUN) / urea, cystatin C, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, total bilirubin, conjugated and unconjugated bilirubin, triglycerides (TG), lactate dehydrogenase (LDH).

2.3.4. Vital signs

Vital signs (systolic and diastolic blood pressure in supine position, pulse rate) will be measured and recorded prior the contrast agent injection, at 30 ± 5 minutes and the day after injection.

2.3.5. Concomitant medications

Concomitant medications will be recorded at the time of informed consent form signature until end of the study.

2.4. Other criteria

None.

3. STATISTICAL METHODS

3.1. General considerations

After the database lock, the statistical analysis will be performed by a CRO under the supervision of Guerbet Biostatistician on the basis of the present document.

A quality control of the statistical analysis will be performed both by the CRO and the sponsor to ensure the reliability of the results.

The GUERBET validation strategy will be described in the Statistical Analysis Validation Plan which will be based on this present document.

Thorough description of all parameters reported will be presented separately by group (HCC/Not HCC) defined by the standard of reference. Summary tabulated results will be provided overall and by assessment time, if relevant or they will be replaced by the corresponding individual data listings if too few patients are concerned.

Tabulations of quantitative parameters will include the following summary statistics: Number of Patients / Mean / Standard Deviation / Minimum / Median / Maximum. If for a given parameter, the raw value has been collected with x decimal places, the mean, median and standard deviation will be rounded to $x + 1$ decimal places, while the minimum and maximum values will be tabulated as reported with x decimal places.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective group. Percentages will be rounded to one decimal place. The category "missing" will be displayed only if there are actually missing values. Percentages will be calculated on the total of non-missing values.

Both experts will provide evaluation for qualitative evaluations of P03277 imaging. In case of consensus meeting, the qualitative evaluations may be modified and will be replaced for analyses by expert reader (except data at delayed phases 1h and 2h).

SAS® Version 9.4 will be used for all descriptive summaries and inferential analyses.

3.2. Null and alternative hypothesis

Not applicable in this study.

3.3. Determination of sample size

As a proof of concept study, no statistical test is planned. Patients' data will be analyzed with descriptive statistics investigating the potential efficacy of P03277 in the liver for the diagnosis of HCC, by dose.

[redacted] In total, 40 patients will be included in this study:

- First, 30 patients in a first cohort with a P03277 dose of 0.1 mmol/kg
- Then 10 patients in a second cohort with a P03277 dose of 0.05 mmol/kg.

3.4. Adjustment for covariates

Not applicable.

3.5. Handling of dropouts or missing data

No imputation or replacement of missing data will be carried out. However, in case of missing data leading to a doubt in the classification of treatment-emergence, the event will be considered as treatment emergent.

3.6. Interim analyses and data monitoring

Safety analysis will be performed for signal detection during the trial.

3.7. Multicenter studies

Only the number of included patients will be presented for each center.

3.8. Multiple comparisons/Multiplicity

Not applicable.

3.9. Use of an “efficacy subset” of patients

If the Per Protocol Set defined in Section 5.2 differs from the Full Analysis Set by more than 10%, secondary efficacy analyses will be repeated for this set.

3.10. Active control studies intended to show equivalence

Not applicable.

3.11. Examinations of subgroups

None.

[redacted]

5. STATISTICAL AND ANALYTICAL PLANS

5.1. Disposition of patients

Patient disposition will be based on all patients who have signed their inform consent form and tabulated by dose and overall for the following categories:

- Total number of patients screened;
- Number (percentage) of patients exposed to P03277;
- Number (percentage) of patients completing the histopathology (V4) visit;
- Number (percentage) of patients completing the study;
- Number (percentage) and reasons of patients screen-failed;
- Number (percentage) and reasons of patients prematurely discontinuing the study;

5.2. Data Sets Analysed and protocol deviations

Data sets analysed

There will be four patient sets and two nodules sets defined for this study:

- The All Patients Set will include all patients who have signed their inform consent form. This set will be used for patient disposition summaries and individual listings.

- The Safety Set (SS) will include all patients who received at least one injection of P03277, regardless of the quantity. This set will be used for evaluation of safety and description of demographic data and baseline characteristics.

- The Full Analysis Set (FAS) will include all patients who undergone P03277 imaging and with at least one standard of reference. This set will be used for description of demographic data and baseline characteristics.

- The Full Analysis Set Nodules (FASN) will include all nodules with available P03277 imaging and with a standard of reference. This set will be used for evaluation of efficacy.

- The Per Protocol Set (PPS) will include all patients with at least one nodule in PPSN.

- The Per Protocol Set Nodules (PPSN) will include all nodules from the FASN who do not present any major protocol deviations or for whom the patient does not present any major deviation. Major deviations will be defined as having an impact on the primary efficacy criteria. Primary analysis will be repeated on this set.

The number of patients by analysis set will be tabulated by dose and overall.

The following table summarizes how the above defined patients sets will be used in the different analyses conducted.

Analyses Sets	All Patients Set	Safety Set	Full Analysis Set (FAS)	Per Protocol Set (PPS)
Disposition	✓			
Demographics and Baseline characteristics		✓	✓	
Exposure		✓		
Efficacy assessment : Primary criterion			✓	✓
Efficacy assessment : Secondary criteria			✓	✓*
Safety assessment		✓		
Listings	✓			

* If there is a difference higher than 10% between the number of patients in FAS and in PPS

Protocol deviations

As per ICH E3 guideline, a protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol, with or without impact to the patient safety or the efficacy assessments. Protocol deviations are to be displayed in the Clinical Study Report (CSR) as a metric of the feasibility and reliability of the study. Protocol deviations are deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.
The list of protocol deviations presented in the CSR is defined in this document but protocol deviations can be added during the Data Review Meeting (DRM). Protocol deviations will be extensively sought from monitoring files, clinical database and external vendors of off-site data (Imaging, Laboratory data…)
Protocol deviations will be split in major and non-major deviations. A major deviation is defined as a deviation having an impact on the primary criterion (e.g. P03277 wrong volume administered to the patient differing of more than 10% from the calculated one). A first categorisation is done in this

document, then categorisation will be confirmed at the DRM before the data base lock blinded as far as possible and any change will be duly described in the meeting minutes.

The deviations are listed in the table below:

Category	Description	Source	Status impact on Primary endpoint
Inclusion criteria not met/ Non-Inclusion criteria met and patient included	Inclusion criteria 1 not met: patient not having reached legal age for participation	Clinical database	Non major
	Inclusion criteria 2 not met: patient not able or willing to participate (no data should appear in the clinical database in this case)	Clinical database	Major
	Inclusion criteria 3 not met: Inform Consent not signed (no data should appear in the clinical database in this case)	Monitoring	Major
	Inclusion criteria 4 not met: patient who do not present any cirrhosis or chronic liver disease	Clinical database	Major
	Inclusion criteria 5 not met for patients who do not present any nodule at the time of inclusion	Clinical database and monitoring	Major
	Inclusion criteria 5 not met for patients presenting more than 3 nodules	Clinical database and monitoring	Non major
	Inclusion criteria 5 not met for patients presenting nodules of more than 3cm and less than 4cm	Clinical database	Non major
	Inclusion criteria 5 not met for patients presenting nodules of more than 4cm	Clinical database	Major for nodule
	Inclusion criteria 5 not met for patients for whom no imaging data was available within 21 days before imaging	Clinical database	Non major
	Inclusion criteria 5 not met: patients for whom nodule(s) was (were) already treated	Monitoring	Major for nodule
	Inclusion criteria 6 not met: Female patient not using a medically approved contraception method* detailed below or be surgically sterilized or post-menopausal (>12 months amenorrhea)	Clinical database and monitoring	Non major
	Inclusion criteria 7 not met: Patient not affiliated to national health insurance according to local regulatory requirement	Clinical database and monitoring	Major
	Non-inclusion criteria 1 met: Pregnant or breast-feeding female patient (a female patient of childbearing potential or with amenorrhea for less than 12 months must have a negative urine or serum pregnancy test within 24 hours prior to study MRI)	Clinical database and monitoring	Non major
	Non-inclusion criteria 2 met: Patients presenting with hepatic nodule more than 3cm in addition to nodule(s) less than or equal to 3cm	Clinical database	Non major

Category	Description	Source	Status impact on Primary endpoint
	Non-inclusion criteria 3 met: Patient already treated for HCC by surgery or thermal ablation for which the resection or coagulation area is less than 2cm from the new nodule(s)	Clinical database and monitoring	Major for nodule
	Non-inclusion criteria 4 met: Patient already treated by chemoembolization	Clinical database and monitoring	Major
	Non-inclusion criteria 5 met: Moderate/severe renal impairment based on measurement done within the 7 days before administration, assessed after iodinated contrast agent administration, or with ESRD	Clinical database	Non major
	Non-inclusion criteria 6 met: Patient with known class III/IV congestive heart failure according to the New York Heart Association classification	Clinical database and monitoring	Non major
	Non-inclusion criteria 7 met: Patient having received or scheduled to receive any contrast agent within 7 days before P03277 planned administration date and within 3 days after P03277 planned administration date	Clinical database and monitoring	Non major
	Non-inclusion criteria 8 met: Patient with known contra-indication(s) to the use or with known sensitivity to drugs from a similar pharmaceutical class as P03277	Clinical database	Non major
	Non-inclusion criteria 9 met: Patient having received any investigational medicinal product within 7 days prior to P03277 planned administration date	Clinical database	Non major
	Non-inclusion criteria 10 met: Patient presenting with any contraindication to MRI examination (see recommendations of the French Society of Radiology)	Clinical database and monitoring	Non major
	Non-inclusion criteria 11 met: Patient having planned palliative/treatment interventions for the suspected nodules (radiotherapy, chemotherapy or others) during the study period except for biopsy/surgery	Clinical database and monitoring	Non major
	Non-inclusion criteria 12 met: Patient related to the investigator or any other study staff or relative directly involved in the study conduct	Clinical database and monitoring	Non major
	Non-inclusion criteria 16 met: Vulnerable patient according to article L1121-6 of the French Public Health Code, (no data should appear in the clinical database in this case)	Clinical database and monitoring	Major
	Non-inclusion criteria 17 met: Patient under guardianship or unable to give his/her consent according to the article L1121-8 of the French Public Health Code (no data should appear in the clinical database in this case)	Clinical database and monitoring	Major

Category	Description	Source	Status impact on Primary endpoint
Treatment deviation	Patient not administered with P03277	Clinical Database	Major
	Volume of contrast agent actually administered is different from theoretical one from 10 to 20%	Clinical Database	Non major
	Volume of contrast agent actually administered is different from theoretical one from more than 20%	Clinical Database	Major
	Theoretical injection rate not respected actually	Clinical Database	Non major
	Power injector not used	Clinical Database	Non major
	Saline flush volume administered not at minimum of theoretical volume	Clinical Database	Non major
	Saline flush volume administered not equal to theoretical volume	Clinical Database (prior amendment 2)	Non major
	Extravasation	Clinical Database	Major
	Location of injection is not adequate	Monitoring	Non major
	Deviation in IMP storage	Monitoring	Non major
Missing data	Lack of source document on-site about standard of reference (imaging or histology)	Monitoring	Major for nodule
	Standard of reference by nodule not available: nodule diagnostic not provided by previous imaging or histology	Clinical database	Major for nodule
	Age is missing	Clinical database	Non major
	Sex is missing	Clinical database	Non major
	Height is missing	Clinical database	Non major
	Race is missing	Clinical database	Non major
	Weight is missing	Clinical database	Non major
	Pregnancy test is missing	Clinical database	Non major
	Physical examination not performed	Clinical database	Non major
	Missing answer to previous intolerance to contrast agent administration	Clinical database	Non major
	Chronic liver disease history missing	Clinical database	Non major
	Child-Pugh score missing	Clinical database	Non major
	Suspected nodule(s) detection procedure missing	Clinical database	Non major

Category	Description	Source	Status impact on Primary endpoint
	Suspected nodule characterization missing	Clinical database	Major for nodule
	AFP value missing	Clinical database	Non major
	Vital signs not measured/missing	Clinical database	Non major
	eGFR result missing	Clinical database	Non major
	Blood sample for central laboratory assessment not performed	Clinical database	Non major
	Laboratory biochemistry results missing	Laboratory database	Non major
	Laboratory hematology results missing	Laboratory database	Non major
	VAS questionnaire not completed while patient reported pain	Clinical database	Non major
	Tolerance at injection site not performed	Clinical database	Non major
Non respect of study schedule and procedures	Forbidden concomitant medication (Any other contrast agent should not be administered with 7 days before and 3 days after P03277 administration)	Clinical database	Non major
	Palliative/treatment interventions for the suspected nodules (radiotherapy, chemotherapy or others)	Monitoring	Non major
	Informed consent date not in 7 days before P03277 injection	Clinical database	Non major
	End of study visit is not V3 or V4 but the last CT exam date used for standard of reference evaluation	Monitoring	Non major
	Blood samples collection for laboratory data not performed at scheduled time	Clinical database	Non major
	Vital signs not measured after a rest of 10 minutes in supine position	Monitoring	Non major
	Vital signs at V2 not taken at scheduled time	Clinical database	Non major
	SAE/AESI not reported within expected timelines	Monitoring	Non major
	Date of histology is more than 2 months before P03277 or more than 13 weeks after	Clinical database	Non major
	Visit not performed at scheduled time	Clinical database	Non major
	Fasting status of the patient was not respected for lab sample	Monitoring	Non major
Deviation from the MRI procedures and evaluations	Missing arterial phase or portal and delayed phase, or pre-contrast	Clinical database /Imaging QC	Major
	Missing MRI on-site evaluation	Clinical database	Non major

Category	Description	Source	Status impact on Primary endpoint
	Missing MRI expert reading evaluation: nodule intensity relative to parenchyma, presence of wash-out and final proposed diagnosis	Expert reading database	Major for nodule
	Missing MRI expert reading evaluation other than the major evaluations	Expert reading database	Non major
	Inadequate time between contrast agent injection and acquisition of triphasic sequences: arterial Phase: more than 2 minutes, portal and delayed phases: more than 8 minutes.	Clinical database / Imaging QC report	Major
	Deviation in time between contrast agent injection and acquisition of triphasic sequences: not 70-80 sec post injection for portal phase, not 3 min post injection for delayed phase other than the major evaluations	Clinical database	Non major
	Deviation in time between contrast agent injection and acquisition of additional sequences: not 15 +/- 5 min for very delayed phase	Clinical database (after amendment 2)	Non major
	Deviation in time between contrast agent injection and acquisition of additional sequences: not 20 min for very delayed phase	Clinical database (prior amendment 2 and first 5 patients)	Non major
	Deviation in time between contrast agent injection and acquisition of additional sequences: not 1 hour for very delayed phase	Clinical database (prior amendment 2 and first 5 patients)	Non major
	Deviation in time between contrast agent injection and acquisition of additional sequences: not 2 hours for very delayed phase	Clinical database (prior amendment 2 and first 5 patients)	Non major
	Any other deviations in time of acquisition of sequences different from protocol	Monitoring	Non major
	Standard procedures for acquisitions were completed in the CRF as not respected	Clinical database	Non major
	Standard procedure for acquisition parameters were not respected according to imaging QC	Imaging QC report	Non major
	Review of reasons for non-adequacy of images for evaluation reported by expert readers or investigators	Clinical/ Reading Database	Non major
	Different MRI machines used during the study	Monitoring	Non major

Category	Description	Source	Status impact on Primary endpoint
GCP deviation	Source document management not appropriate	Monitoring	Non major
	Inappropriate process of images de-identification	Monitoring	Non major

When the deviation is only applicable to nodules, the nodule presenting at least one major protocol deviation will be excluded from the PPSN.
Frequency and percentages of patients with protocol deviations, also number of nodules with major protocol deviations, will be presented by dose and overall breaking down by status (major/non major). A listing of all protocol deviations will also be provided breaking down by centre in CSR appendix 16.2.2 and major protocol deviations will be flagged.

5.3. Measurements of study drug compliance

Study drug compliance in this study refers to the injection of P03277. The compliance will be computed in terms of percentage by

$$Compliance = \frac{actual\ volume - theoretical\ volume}{theoretical\ volume} \times 100$$

Number of patients with theoretical volume to be administered not equal to the one actually administered will be presented. Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for difference between actual and theoretical and volumes of study product and displayed by dose. Frequency and percentage will be calculated for differences between volumes (< -10%, ≥ -10% and < 0 %, > 0% and ≤ 10%, >10%).

5.4. Demographic and Other Baseline Characteristics

The analysis will be done using the Safety Set and the Full Analysis Set.

5.4.1. Demographic data

Demographic parameters are age, sex, childbearing potential, body weight in kilograms (kg), height in centimetres (cm), body mass index (BMI in kg/m²) and ethnic origin (self-reported race/ethnicity).

Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for age, body weight, height and BMI and displayed by dose and overall. Frequency and percentages will be calculated for age (≥18 and <65, ≥65), sex and BMI (<18.5, ≥18.5 and <25, ≥25 and <30, ≥30).

5.4.2. Study disease

Chronic liver disease status at inclusion visit will be displayed by dose and overall:

Frequency and percentages of parameters supporting the diagnosis of chronic liver disease (biopsy, endoscopic, biological, ultrasound, elastography, other) will be presented.

Frequency and percentages of parameters supporting the aetiology of chronic liver disease (alcohol, HBV, HCV, non-alcoholic-NASH, other) will be presented.

Frequency and percentages will be presented for each class of the Child Pugh score calculated on the last evaluation available. The classes are defined as follows:

- A: well-compensated disease (score between 5 and 6)
- B: significant functional compromise (score between 7 and 9)
- C: decompensated disease (score between 10 and 15).

5.4.3. Risk factors

Not applicable.

5.4.4. Medical history and concomitant diseases

Medical history and concomitant diseases will be coded in System Organ Classes (SOC) and preferred terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1.

Summary tables (number and % of patients) grouped by SOC and PT will be presented by dose and overall for Medical history firstly then for concomitant diseases. Medical histories are those "Not Ongoing" and concomitant diseases are those "Ongoing" at the screening visit.

Listing of demographics, study disease characteristics and all diseases will be presented in CSR Appendix 16.2.4 with a flag for ongoing diseases.

5.4.5. Clinical laboratory evaluation at baseline

Laboratory data analysis will be done using the safety set by dose and overall. Blood samples will be performed during screening visit.

Results will be presented in standard international (SI) units and conventional United States units (See Table 1 and Table 2 respectively). Original units will only be listed if different. Laboratory data will be analyzed quantitatively and qualitatively. Qualitative analyses will be done via comparison of laboratory data to their reference ranges. Quantitative analyses will be done by tabulating raw data.

Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for baseline serum creatinine and eGFR and displayed by dose and overall.
Technique used to determine serum creatinine level and eGFR method will be presented.
Table of locally eGFR and baseline serum creatinine will present the results in standard international units and conventional United States units.

Qualitative analysis of eGFR will be done via comparison of data to the reference ranges (<60, ≥60 and ≤90, >90).

5.4.6. Vital signs, physical findings and other observations related to safety at baseline

A routine physical examination will be performed at baseline, including the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological.
Physical examination will only be listed in CSR appendix 16.2.4.
If any abnormality is detected among those parameters, it will be described in the Medical History section.

5.4.7. Prior therapies

Prior therapies are defined as therapies ended before administration.
Prior medications will be coded using the WHODRUG dictionary version June 2015.
The number and percent of patients taking prior therapies will be presented by dose and overall.

Summary tables (number and % of patients) grouped by the first and the fourth level of ATC code will be presented by dose and overall for prior medication.

5.4.8. Other baseline characteristics

5.4.8.1 Contrast agent history

Data concerning contrast agent history will be only listed in section 16.2.4.

5.4.8.2 Suspected nodule detected

Suspected nodules detection will be described by dose and overall using the FAS.

Frequency and percentage of procedure that first detected will be presented.

Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated time between the procedure and IMP administration (days).

5.4.8.3 Suspected nodule characterization

Suspected nodule(s) characterization will be displayed by procedure for each dose and overall using the FAS:

- Procedure performed: Yes; No
- If yes:
    - Number of suspected nodule(s)
    - Time between the procedure(s) and IMP administration (days).

5.4.8.4 Pregnancy test

Pregnancy test will be only listed in section 16.2.4.

5.4.8.5 Histologic analysis

Histologic analysis scheduled will only be listed in CSR appendix 16.2.4.

5.4.8.6 MRI Examination

MRI examination and characteristics includes the following parameters and will be presented by dose using the FAS:

- MRI performed: Yes; No.
- If yes:
    - Time between the previous imaging, last date if several procedures performed, and trial MRI examination (days)
    - Magnetic field strength (Tesla): 1.5T; 3.0T
    - Occurrence of any deviation from the MRI procedures (Yes; No; If yes, Specification (multiple choices): Scanner-related deviation; Subject-related deviation
- Unenhanced MRI and contrast-enhanced MRI sequences performed: Yes; No
- If yes:
    - Time between the injection of contrast agent and each phase post-injection
- Reasons for missing data at unenhanced MRI and contrast-enhanced MRI sequences as per expert reader by dose: Not available; Not assessable

Subtraction sequences available at contrast-enhanced MRI sequence on arterial phase as per expert reader by dose if at least one hyperintensity for contrast intensity relative to parenchyma at 3D GRE T1-WI with fat saturation: Yes; No.

5.5. Efficacy evaluation

Efficacy data will be summarized by dose using the FAS/FASN and PPSN for primary efficacy analysis and only using FAS/FASN for any other efficacy analysis. If there is a difference higher than 10% between the FAS and PPS then the secondary analysis will be repeated on the PPS.
Listing of all efficacy data will be presented in CSR appendix 16.2.6.

5.5.1. Primary analysis of the primary criteria

P03277 imaging diagnosis (HCC or not HCC) will be presented at nodule level in a contingency table displaying number for each diagnosis category (HCC or not HCC) obtained with the standard of reference according to the following table:

		Standard of reference		
		HCC	Not HCC including uncertain cases	
P03277 imaging expert reading results	HCC (Typical features on this MR examination)	True positive *n1*	False positive *n2*	Total *n1 + n2*
	Not HCC (No nodule/atypical features)	False negative *n3*	True negative *n4*	Total *n3 + n4*
		Total *n1 + n3*	Total *n2 + n4*	All total *N*

In case of nodules with a standard of reference but no detected by the experts, the diagnostic of expert reading will be considered Not HCC to complete the contingency table.

The following parameters will be calculated:

- Sensitivity: the number of nodules showing true positive HCC (i.e. HCC detected with both P03277 imaging and Standard of reference) divided by all nodules considered HCC according to standard of reference (*n1 / n1 + n3*)
- Specificity: the number of nodules showing true negative HCC (i.e. HCC detected neither with P03277 imaging nor with Standard of reference) divided by all nodules considered as not HCC or uncertain according to standard of reference (*n4 / n2 + n4*)
- Accuracy: the number of nodules showing true positive HCC and true negative HCC over all nodules (*n1 + n4 / N*)
- Positive predictive value: the number of nodules showing true positive HCC /all nodules showing HCC according to P03277 imaging (*n1 / n1 + n2*)
- Negative predictive value: the number of nodules showing true negative HCC /all nodules not showing HCC according to P03277 imaging (*n4 / n3 + n4*).

Frequency and percentages of nodule diagnosis used for standard of reference (HCC/not HCC) will be presented.

5.5.2. Supportive analyses of primary criterion

Nodule characterization from previous contrast enhanced imaging for diagnostic (CT and/or MRI), mapping and measurement will be described by dose:

At nodule level, typical imaging hallmark and hyperintensity of parenchyma relative to the nodule will be presented. Frequency and percentages of suspected nodule(s) characterization depending the procedure will be described.

Frequency and percentages of localization code of segment of suspected nodule(s) will be presented. Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated size of nodule (mm).

Previous alpha-fetoprotein (AFP) value will be analyzed quantitatively and qualitatively. Frequency and percentages will be presented for previous AFP (≤200 ng/mL, >200 ng/mL).

Diagnosis used for standard reference from previous contrast enhanced imaging and AFP will be described.

Nodule characterization from histopathology will be presented for patients who performed a biopsy:

- time between MRI examination and the procedure(s) (days)
- nodule diagnosis by assessment, including final assessment.

Nodule diagnosis (HCC, not HCC) according to histopathology and according to previous imaging will be presented.

Nodule diagnosis based on experts reading or consensus will be described.

5.5.3. Additional analyses of primary criterion

Not Applicable.

5.5.4. Analysis of secondary criteria

Tables from expert reading will be displayed by expert readers.

Results of consensus will be listed presenting patient number, dose, nodule number and diagnosis.

Technical adequacy of images (on-site and/or expert reading)
Technical adequacy will be presented by reading type, by displaying number and frequency of adequate and inadequate images and the categories for inadequacy. Number of cases not assessable and assessable will be presented.

Visualization of biliary and liver vascular abnormalities (expert reading)
Biliary and liver vascular abnormalities will be presented globally, by displaying number and frequency of portal thrombosis, hepatic venous thrombosis, biliary tract invasion, and visualization of arterio-portal fistula, and if yes, close to which nodule(s).

Number of nodules evaluated (on-site and/or expert reading)
Number of nodules evaluated by P03277 imaging will be presented quantitatively and qualitatively at patient level.

Localization and size of suspected nodule(s) (on-site and expert reading)
Frequency and percentages of localization code of segment of suspected nodule(s) will be presented on-site and by expert readers. Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated size of nodule (mm).

Qualitative evaluation of nodule intensity and nodule description (expert reading)
Qualitative evaluation of nodule intensity (hypointensity, hyperintensity, isointensity and hetero/homogeneous) relative to parenchyma at each phase (T2, T1 unenhanced, arterial, portal, delayed) as well as, presence of capsule (portal and delayed phases), wash-out, visualization of fat and iron presence (T1 in and opposed phase) will be presented by displaying number and frequency for each standard of reference group (HCC or not HCC).

Quantitative evaluation of nodule intensity (on-site)
Quantitative evaluations of nodule intensity (SI, SNR, CNR and PE) will be presented at each phase (T1 unenhanced, arterial, portal, delayed, 15 ±5 minutes) for each standard of reference group (HCC or not HCC) by displaying number [n], mean, standard deviation [SD], median, minimum, maximum.

Quantitative evaluation of vascular intensity (on-site)
Quantitative evaluations of aorta intensity and portal vein intensity (SI and SNR) will be presented at patient level globally by displaying number [n], mean, standard deviation [SD], median, minimum, maximum.

Qualitative evaluation at very delayed sequences for visualization of the parenchyma enhancement and nodule enhancement relative to parenchyma (expert reading)
In case no more than 5 patients received very delayed sequences, data will be presented as listings only.
Qualitative evaluation of parenchyma intensity relative to that on unenhanced GRE T1 sequence with fat-suppressed (hypointense, isointense or hyperintense) will be presented globally showing number and frequency at three available very delayed images and sequences (15 ±5 minutes, 1h, 2h).

Qualitative evaluations for nodule enhancement relative to parenchyma (hypointense, isointense or hyperintense) will be presented by displaying number and frequency for each reference group (HCC or not HCC).

5.6. Safety Evaluation

Safety analysis will be done using the safety set presented by dose and overall.

5.6.1. Extent of Exposure

Duration from inclusion visit to IMP administration, summary of durations during the study, mode of injection, location of the injection site, volume theoretically administered, volume actually administered, dose administered, occurrence of an overdose, actual rate of administration and volume of saline flush will be tabulated.

All durations will be computed in days as second date of interest - first date of interest + 1.

Listing of exposure will be presented in CSR appendix 16.2.5.

5.6.2. Adverse Events

Adverse events (AEs) will be coded using MedDRA version 20.1.

The time period for the assessment of AEs will be divided into 3 mutually exclusive and exhaustive periods:

- before start time of administration of P03277
- after start time of administration of P03277 until day + 1 safety follow-up
- after safety follow-up (> day +1) until biopsy if it is done

Events will be classified as treatment-emergent adverse event (TEAE) if they occurred after the start time of P03277 administration.

Partial start dates/times will be queried. If there is any doubt about treatment emergence, AEs will be classified as treatment emergent.

Overall summary:
The number (%) of patients and number of events will be presented in an overall summary for all AEs, AEs occurring before start time of P03277 administration and then all TEAEs according time periods by dose including:

- Total number of AEs
- Total number of patients with at least one AE
- Distribution of the number of AEs reported by patients
- Total number of TEAEs
- Total number of patients with at least one TEAE
- Total number of serious AEs
- Total number of patients with at least one serious AE
- Total number of AEs according to intensity
- Total number of patients with at least one AE according to intensity
- Total number of AEs according to outcome
- Total number of patients with at least one AE according to outcome
- Total number of AEs requiring AE-targeted medication
- Total number of patients with at least one AE requiring AE-targeted medication
- Total number of AEs requiring other AE-targeted action
- Total number of patients with at least one AE requiring other AE-targeted action

with the addition of the following information for TEAEs:

- Total number of AEs with relationship to IMP/ a study procedure
- Total number of patients with at least one AE with relationship to IMP/ a study procedure
- Total number of AEs according to action taken with regard to administration of the IMP
- Total number of patients with at least one AE according to action taken with regard to administration of the IMP

The number (%) of serious events will be presented according to the following criteria:

- Death
- Life-threatening

- Hospitalisation or prolongation of hospitalisation
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Medically important.

Distribution of AEs
A table will present the total numbers and the distribution of AEs (number [%] of patients with 1, 2, etc… AEs).

Summaries by SOC and PT
The table of summaries of at least one TEAE will be displayed by SOC and PT by dose and overall. Same table of summaries will be displayed for at least one TEAE with relationship to IMP/a study procedure by dose and overall.

Data listings will present all AEs reported, including non-TEAEs. Adverse event listings will be sorted by site, patient number and dose and will also display the SOC, and PT, time of onset, duration, intensity, seriousness, outcome, relationship to the IMP, relationship to a study procedure, action taken with IMP, AE-targeted medication, other AE-targeted action, date and time of IMP administration (presented in CSR appendix 16.2.7).

AE Duration will be computed in days as Date of End of AE - Date of Onset of AE + 1. If the AE started before administration or after safety follow-up, no date and time of administration will be displayed.

5.6.3. Deaths and other serious adverse events

All serious adverse events experienced during the study will be separately listed per patient number and dose, presenting: description, SOC, PT, start and end date, duration, intensity, the relationship to study drug, the action taken, the outcome, the seriousness criteria, date and time of IMP administration, study period.

5.6.4. Clinical laboratory evaluation

All laboratory values recorded during the study will be individually listed and flagged for values outside reference ranges and clinically significant (presented in CSR appendix 16.2.8).

Each hematology and biochemistry parameter will be tabulated for each visit presenting also abnormal values.

Tables will present the results in standard international units and United States units (See Table 1 Hematology parametersTable 1 and Table 2). Standard international units, United States units and original units (if different) will be listed.

The baseline is defined as measure collected at visit 1 or visit 2.
Laboratory data will be analyzed quantitatively and qualitatively. Qualitative analyses will be done via comparison of laboratory data to their reference ranges. Any significance will be monitored and reported either as MH or AE. Quantitative analyses will be done by tabulating raw data and change from baseline. They will be displayed qualitatively as well as by means of shift tables for creatinine

(<60, ≥60 and <100, ≥100), eGFR (<30, ≥30 and <60, ≥60 and <90, ≥90) and BUN (<3, ≥3 and <8, ≥8) for post-baseline visit as compared to the baseline value.

Table 1 Hematology parameters

Hematology parameters		SI Units	US Units
Basophils	BASO	10^9/L	10^3/µL
Basophils/Leukocytes	BASOLE	%	%
Eosinophils	EOS	10^9/L	10^3/µL
Eosinophils/Leukocytes	EOSLE	%	%
Hematocrit	HCT	v/v	%
Hemoglobin	HGB	g/L	g/dL
Lymphocytes	LYM	10^9/L	10^3/µL
Lymphocytes/Leukocytes	LYMLE	%	%
Mean red blood cells volume	MCV	fL	fL
Monocytes	MONO	10^9/L	10^3/µL
Monocytes/Leukocytes	MONOLE	%	%
Neutrophils	NEUT	10^9/L	10^3/µL
Neutrophils/Leukocytes	NEUTLE	%	%
Platelet count	PLAT	10^9/L	10^3/µL
Red blood cells = Erythrocytes	RBC	10^{12}/L	10^6/µL
White blood cells = Leukocytes	WBC	10^9/L	10^3/µL

Table 2 Biochemistry parameters

Biochemistry parameters		SI Units	US Units
Alpha fetoprotein	AFP	µg/L	ng/mL
Alkaline phosphatase	ALP	U/L	U/L
Aspartate amino transferase	AST	U/L	U/L
Alanine amino transferase	ALT	U/L	U/L
Direct bilirubin	BILDIR	µmol/L	mg/dL
Bilirubin	BILI	µmol/L	mg/dL
Indirect Bilirubin	BILIND	µmol/L	mg/dL
Blood Urea Nitrogen	BUN	mmol/L	mg/dL
Calcium	CA	mmol/L	mg/dL
Chloride	CL	mmol/L	mEq/L
Creatinine	CREAT	µmol/L	mg/dL
Cystatin C	CYSTATC	mg/L	mg/L
Glucose	GLUC	mmol/L	mg/dL
Potassium	K	mmol/L	mEq/L
Lactate dehydrogenase	LDH	U/L	U/L
Phosphate	PHOS	mmol/L	mg/dL
Protein	PROT	g/L	g/dL
Sodium	SODIUM	mmol/L	mEq/L
Triglycerides	TRIG	mmol/L	mg/dL
eGFR	GFRE	mL/min/1.73m²	mL/min/1.73m²

5.6.5. Vital signs, physical findings and other observations related to safety

Raw values and changes from baseline of Systolic/Diastolic Blood Pressure (mmHg) in supine position and Pulse Rate (beats/min) will be described according to the following schedules:

- Immediately prior to contrast agent injection (baseline value)

- At 30±5 minutes following P03277 injection
- One day after P03277 injection

Blood pressure and pulse rate will be measured after a rest of 10 minutes in supine position. Blood pressure will not be measured on the arm used for the injection.

A clinically significant value is defined as follows:

- Pulse Rate < 40 or >100 bpm;
- Systolic Blood Pressure < 90 or >160 mmHg;
- Diastolic Blood Pressure > 100 mmHg.

Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for these parameters, as well as change from baseline. Qualitative analysis will be done via comparison of vital signs data to their normal ranges.

Listings of vital signs will be provided in CSR appendix 16.2.9, including Systolic/Diastolic Blood Pressure (mmHg), Pulse Rate (beats/min), and flag for clinically significant.

Number of patients experiencing burning, pain, eruption, extravasation and inflammation at site injection will be tabulated by dose and overall. Pain at injection site will be measured using the Visual Assessment Scale (VAS) and VAS measurements for these patients will be tabulated.

5.6.6. Concomitant medications

The number and percentage of patients taking concomitant medications will be presented. Summary tables (number and % of patients) grouped by the first and the last level of ATC code (ATC4) will be presented by dose and overall for concomitant medications. Concomitant medications are those ongoing at or started after the P03277 injection.
Listing of all concomitant medications will be presented in CSR appendix 16.2.4.

Concomitant medications will be coded using the WHODRUG dictionary version June 2015.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7. SHELLS FOR TABLES, FIGURES AND LISTINGS

All outputs will be produced using SAS version 9.4 or a later version.

All recorded data will be listed following the table order and structure of the case report form (CRF). In addition, all derived data used in the analyses will be listed. The listings will include all patients and will be ordered by site and patient.

Unless otherwise indicated, in case of continuous or ordinal variables summary statistics are the n, mean, SD, median, minimum and maximum. The mean, median and SD will be reported to 1 decimal more than the data; and minimum and maximum to the same number of decimals as the data. In case of nominal variables, summary statistics are the n and the frequency in terms of percentage.

7.1. Clinical study report in-text tables, figures and listings

7.2. Contents of clinical study report section 14

7.3. Contents of clinical study report section 16.2

8. REFERENCES

[redacted]

9. APPENDICES

Contents of clinical study report section 14: see attached document “GDX-44-008 - SAP - Attachment Tables - version 1.0”.

Contents of clinical study report section 16.2: see attached document “GDX-44-008 - SAP - Attachment Listings - version 1.0”.