Non-Interventional Study Protocol
B3461058

Prevalence and characteristics of transthyretin amyloidosis in patients with left ventricular hypertrophy of unknown etiology
TTRACK

Statistical Analysis Plan
(SAP)

Version: 2

Author: PPD

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ABBREVIATIONS

Abbreviation	Definition
^{99}mTc-DPD	99mTechnetium-3,3-diphosphono-1,2-propanodi-carboxylic acid
^{99}mTc-PYP	99mTechnetium-pyrophosphate
^{99}mTc-HMDP	99mTechnetium-hydroxymethylene diphosphonate
AA	Serum Amyloid A Protein
AE	Adverse event
AICD	Automatic Implantable Cardiac Defibrillator
AL	Light chain amyloidosis
ATTR	Transthyretin amyloidosis
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTRv	Variant transthyretin related amyloidosis
ATTRwt	Wild type transthyretin related amyloidosis
AVA	Aortic valve area
CI	Confidence interval
CM	Cardiomyopathy
CTS	Carpal Tunnel syndrome
ECG	Electrocardiogram
ECHO	Echocardiography
e-CRF	Electronic Case Report Form
FAS	Full analysis set
HCM	Hypertrophic cardiomyopathy
IQR	Interquartile Range
LGE	Late gadolinium enhancement
LV	Left ventricular
LVH	Left ventricular hypertrophy
LVOTO	Left ventricular outflow tract obstruction
MRI	Magnetic resonance imaging
MWT	Maximal wall thickness
NI	Non-interventional
NT-proBNP	N-terminal pro-brain natriuretic peptide
PN	Polyneuropathy
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SCD	Sudden cardiac death
sFLC	Serum Free Light Chain
SOC	System Organ Class
SPECT	Single Photon Emission Computed Tomography
TTR	Transthyretin

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Effective Date	Change Type (New, Revise, Admin)	Summary of Revisions
1	27-Apr-2020	New	
2	06-Jul-2022	Revise	• Wording modified in line with clarifications in protocol amendment 2 • To add sensitiviy analyses to assess the impact of: o using a SPECT o no longer using a centralized lab • Subgroups analyses added • To add scintigraphy discrepancies analysis

2 INTRODUCTION

Note: in this document any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

The main purpose of this study is to determine the prevalence of transthyretin amyloid cardiomyopathy *(ATTR-CM) among patients admitted due to* left ventricular hypertrophy *(LVH) of unknown etiology when radionuclide bone scintigraphy or* single photon emission computed tomography *(SPECT) is used.*

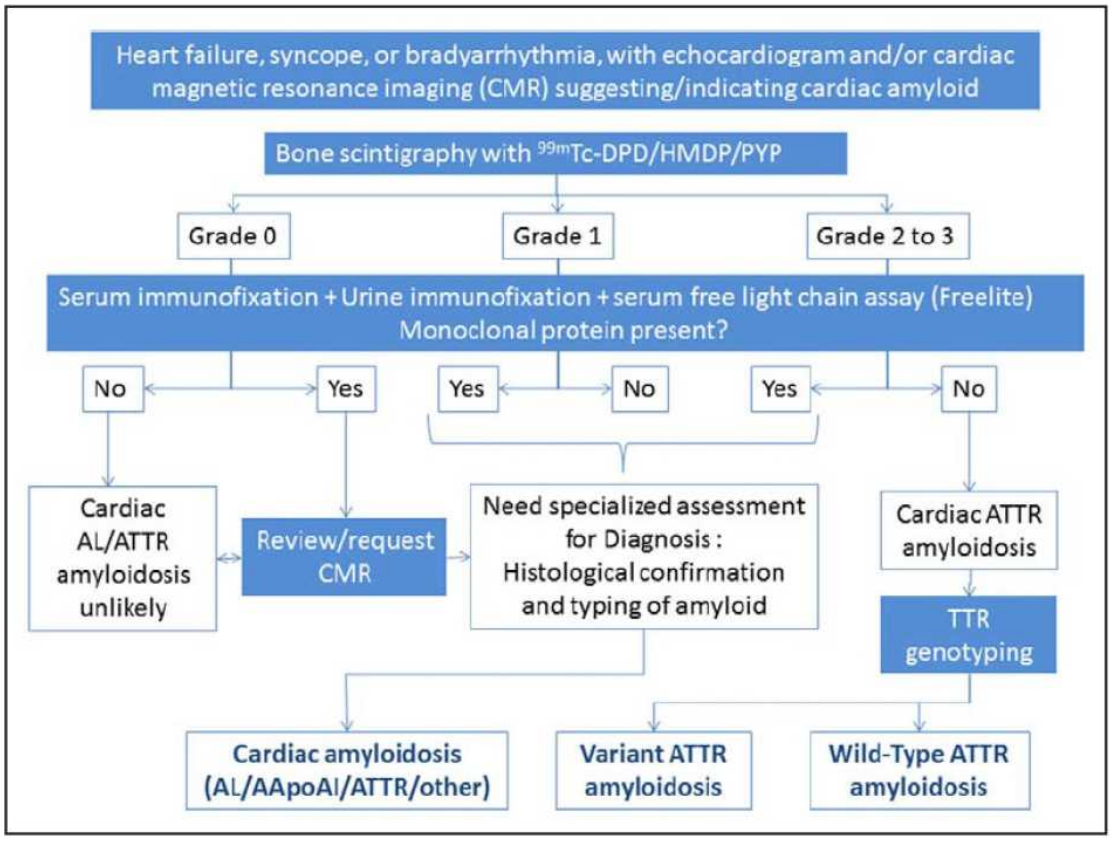

Figure 1. Diagnostic algorithm for patients with suspected amyloid cardiomyopathy (Gillmore 2016).

2.1 STUDY DESIGN

TTRACK is an epidemiological multicenter and multinational study.

Study population

This study will include *patients with LVH from undiagnosed etiology and the following inclusion/exclusion criteria:*

1. Inclusion criteria:

a. *Patient signed inform consent.*

b. *Males and Females.*

c. *Age ≥50 years.*

d. *Left ventricular hypertrophy (LVH) defined as end-diastolic LV maximum wall thickness (MWT) ≥15mm in Echocardiogram.*

e. *Plan to undergo or recently underwent radionuclide bone scintigraphy and/or SPECT with any of the following radio labelled tracers: ^{99m}Tc-DPD or ^{99m}Tc-PYP or ^{99m}Tc-HMDP.*

Scintigraphy will be defined at each site according to the standard grading:
Grade 0 = absent cardiac uptake
Grade 1 = mild uptake less than bone
Grade 2 = moderate uptake equal to bone
Grade 3 = high uptake greater than bone

2. Exclusion criteria

a. *Etiological diagnosis explaining the LVH prior to patient inclusion (eg, Sarcomeric HCM, Myeloma, Fabry disease, Sarcoidosis, any type of amyloidosis [AA, AL, TTR**])*

*** TTR diagnosis at exclusion criteria: Direct relative (siblings or parents) of a carrier with a known hereditary mutation in the TTR gene or any patient already diagnosed by any of the following: cardiac fixation at the bone scintigraphy, TR mutation at the genetic testing, biopsy with amyloidosis (positive red congo) and positive TTR staining.*

b. *Severe aortic stenosis defined as aortic valve area (AVA) < 1.0 cm2*

Data source

Data will come from medical records and will be collected in routine clinical practice. As an epidemiological study, there are no specific requirements with regard to patient procedures to be performed or the treatment regimen. Data from each patient will be reported on an electronic case report form (e-CRF).

Treatment/cohort labels

NA

2.2 STUDY OBJECTIVES

1. Primary objective

- *To assess the prevalence of patients with cardiac fixation at the radionuclide bone scintigraphy and/or Single Photon Emission Computed Tomography (SPECT) performed with 99mTc-DPD or 99mTc-PYP or 99mTc-HMDP* among patients with (left ventricular hypertrophy) LVH from undiagnosed etiology;*

2. Secondary objectives

- *To assess the prevalence of Light Chain Amyloidosis (AL) or Transthyretin amyloid (ATTR) amyloidosis in patients with cardiac fixation at the bone scintigraphy (visual grade 1 to 3) and/or SPECT;*
- *To assess the prevalence of hereditary (ATTRv) and wild-type (ATTRwt) ATTR amyloidosis in patients diagnosed with ATTR amyloidosis;*
- *To describe TTR genetic mutations** in patients with ATTRv amyloidosis;*
- *To assess the prevalence of patients with familial history of known cardiomyopathy (CM), polyneuropathy (PN), sudden cardiac death (SCD) among their relatives (ie, parents, siblings and 2nd/3rd degree grade family members);*
- *To assess the prevalence in patients with cardiac fixation at the bone scintigraphy or SPECT of concomitant signs or symptoms of ATTR amyloidosis, ie,:*
  - *Sensori-motor Polyneuropathy (PN);*
  - *Carpal Tunnel syndrome (CTS);*
  - *Autonomic dysfunction;*
  - *Cardiological manifestations;*
  - *Laboratory signs;*
- *To compare the clinical and biochemical characteristics between patients with positive scintigraphy (cardiac fixation at the bone scintigraphy grade 1, 2 or 3) and/or SPECT;*
- *To assess the level of discrepancy in the evaluation of the scintigraphy and/or SPECT images by different evaluators.*

** Bisphosphonate (99mTc-DPD/99mTc-PYP/99mTc-HMDP) Scintigraphy*
*** Variant and pathogenic mutation by sequencing the coding parts*

3 INTERIM ANALYSES

An interim analysis of the data collected was planned *for all the variables as soon as 75 patients will be selected with a scintigraphy grade 1, 2 or 3 and with completed e-CRF.* This interim analysis was finally not performed.

In addition, an interim analysis was performed for publication purpose, all patients screened until the May 11th 2020 were included in this analysis. Considering the expected number of patients with a scintigraphy grade 1, 2 or 3, all analyses described in this SAP were done, except multivariate analyses planned in 0.

4 HYPOTHESES AND DECISION RULES

4.1 STATISTICAL HYPOTHESES

TTRACK is a non-interventional and uncontrolled study. In that sense, there is no inferential hypothesis that will serve for a claim.

4.2 STATISTICAL DECISION RULES

The analysis of this study will be mainly descriptive. However, factors associated to ATTR will be identified using a multivariate analysis. All statistical tests will be exploratory in nature.

5 ANALYSIS SETS/POPULATIONS

5.1 FULL ANALYSIS SET

Full Analysis Set 1 – Primary population

Full Analysis Set 1 (FAS1) includes all patients who meet eligibility (inclusion/exclusion) criteria and with a radionuclide bone scintigraphy and/or SPECT performed with 99mTc-DPD/99mTc-PYP/99mTc-HMDP.

Full Analysis Set 2 – All FAS1 patients with positive scintigraphy (grade 1, 2 or 3)

Full Analysis Set 2 (FAS2) is a subset of FAS1 patients with grading of cardiac retention equal to grade 1, grade 2 or grade 3.
Analysis of group 1 vs group 2&3 independently and grouped will be performed
Patients with grade 1 will be considered od "undetermined etiology"

Full Analysis Set 3 – All FAS2 patients with positive scintigraphy grade 2 or 3 (Cardiac amyloidosis)

Full Analysis Set 3 (FAS3) is a subset of FAS2 patients with grading of cardiac retention equal to grade 2 or grade 3.

FAS 3.1 Patients with grade 2-3 **without** monoclonal protein abnormalities (ATTR amyloidosis)

FAS 3.2 Patients with grade 2-3 **with** monoclonal protein abnormalities (Undefined etiology, cardiac ATTR amyloidosis, or MGUS or AL Amyloidosis). Monoclonal protein abnormalities if defined as Positive IFE (serum and/or urine) or positive FLC (See definition in section 6.3).

5.2 SAFETY ANALYSIS SET

Safety Analysis Set (SAF) includes all enrolled patients.

5.3 SUBGROUPS

Some secondary endpoints (See table in section 8.2) will also be described by the following subgroup:

- ATTRv: ATTR patients with a ATTR gene sequencing with variant transthyretin will be considered as ATTRv.

- ATTRwt: ATTR patients with a ATTR gene sequencing with a result of « No Mutation » will be considered as ATTRwt

6 ENDPOINTS AND COVARIATES

6.1 EFFICACY/EFFECTIVENESS ENDPOINTS

NA

6.2 SAFETY ENDPOINTS

Adverse events (AE) will be coded using MedDRA version 20.0 or later.

6.3 OTHER ENDPOINTS

Primary endpoint

Patients with cardiac fixation at the radionuclide bone scintigraphy and/or SPECT performed with ^{99m}Tc-DPD or ^{99m}Tc-PYP or ^{99m}Tc-HMDP will be defined as patients with a cardiac retention of grade 1, grade 2 or grade 3.
Patients without cardiac fixation at the radionuclide bone scintigraphy performed and/or SPECT with ^{99m}Tc-DPD or ^{99m}Tc-PYP or ^{99m}Tc-HMDP will be defined as patients with a cardiac retention of grade 0.

Secondary endpoints

1. **Presence of Transthyretin amyloid (ATTR) or patients with suspicion of MGUS / Light Chain Amyloidosis (AL)**

- Patients with grade 2 or 3 at scintigraphy will be considered "Cardiac amyloidosis patients"
  - Patients with grade 2 or 3 at scintigraphy without monoclonal protein abnormalities will be considered patients with **ATTR amyloidosis**
  - Patients with grade 2 or 3 at scintigraphy with monoclonal protein abnormalities will be considered of the population of **patients with suspicion of MGUS or AL amyloidosis**
- Patients with grade 1 at scintigraphy will be considered as **"undetermined"**

Monoclonal protein abnormalities are defined as patients with positive IFE (Immunofixation electrophoresis) (serum and urine) or with abnormal FLC (free light chain) ratio:

	eGFR			
	>60	**45-<60**	**30-<45**	**<30**
Abnormal FLC ratio	≥1.65	≥1.92	≥2.06	≥2.17
Normal FLC ratio	<1.65	<1.92	<2.06	<2.17

eGFR will be calculated with MDRD formula:
GFR (mL/min/1.73 m²) = 175 × (Serum $_{creatinine}$)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American) (conventional units)

2. Presence of hereditary (ATTRv) and wild-type (ATTRwt) ATTR
ATTR patients with a ATTR gene sequencing with variant transthyretin will be considered as ATTRv.
ATTR patients with a ATTR gene sequencing with a result of « No Mutation » will be considered as ATTRwt.

3. Presence of familial history of known cardiomyopathy (CM), polyneuropathy (PN), sudden cardiac death (SCD)
Family history for each disease will be considered for 1st degree parent, siblings and 2nd/3rd grade family.

4. Senso-motor Polyneuropathy
Patients with at least one red flag in the neurological part of the ATTR-Amyloidosis red flags e-CRF part will be considered as patients with a senso-motor Polyneuropathy.

5. Carpal Tunnel syndrome (CTS)
Patients with a CTS will be patients with a bilateral or unilateral CTS.
Patients without CTS will be patients with a "NO" to the question "Carpal tunnel syndrome symptoms"

6. Autonomic dysfunction
Patients with autonomic dysfunction will be patients with at least one autonomic sign or autonomic symptom = "Yes"

7. Cardiological manifestations
Patients with cardiological signs will be defined as patients with at least one of the following criteria fulfilled:

Criterion	Value
In Cardiological assessments part of the e-CRF	
Atrial Fibrillation	Yes permanent
Pacemaker	Yes
AICD	Yes
In MRI part of the e-CRF	
LGE	Positive
In ECG part of the e-CRF	
Sinus rhythm	No
PR interval	< 80 ms or > 350 ms
QRS interval	< 60 ms or > 250 ms
Sokolow index	< 1 mm or > 70 mm
Pseudo-MI pattern	Yes
PPOr precordial R wave progression	Yes
LBBB	Ticked
RBBB	Ticked
Paced	Ticked
Intraventricular conduct delay	Ticked
LVOT	Yes
If longitudinal strain is done, strain apical preserved	Yes
LV end-diastolic diameter	< 20 mm or > 80 mm
MWT	< 15 mm or > 100 mm
MWT at septum	< 3 mm or > 50 mm
MWT posterior wall	< 3 mm or > 50 mm
LV mass index	< 40 g/m² or > 160 g/m²
Maximal aortic velocity	> 5 m/s
Mean gradient of Aortic valvular stenosis	> 70 mmHg
Area of Aortic valvular stenosis	< 0.2 cm² or > 3 cm²

8. Laboratory signs

Patients with at least one blood test laboratory result out of range will be considered as patients with laboratory signs.

- For creatinine, patients with a value lower than 45 µmol/L or higher than 104 µmol/L will be considered as out of range
- For haemoglobin, patients with a value lower than 11,5 g/dL or higher than 16. g/dL will be considered as out of range
- For BNP, patients with a value higher than 100 pg/mL will be considered as out of range
- For NTproBNP, patients with a higher than 125 pg/mL will be considered as out of range
- For Troponin I, patients with a value higher than 26 pg/mL will be considered as out of range

- For Troponin T, patients with a value higher than 14 pg/mL will be considered as out of range

9. Coexistence of typical neurological signs / symptoms

Patients with only one redflag / patients with two redflags / patients with at least three redflags.

6.4 COVARIATES

- Grade (0, 1, 2, 3) and for grade 2&3 pooled together
- Age in class 50 – ≤60 ; >60 – ≤70 years ; >70 – ≤80 years ; > 80 years]
- Gender (Male/Female)
- Cardiological symptomatology (Yes/No, where patient with a cardialogical symptomatology are defined as patient with a least one cardiological manifestation (point 7 in 0)
- High Creatinine, high BNP and high NTproBNP (See Section 6.3, § 8)

7 HANDLING OF MISSING VALUES

Missing data will not be imputed.

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

Quantitative variables will be described using number of filled and missing data, mean, standard deviation, median, 1st and 3rd quartiles, minimum and maximum. The 95%CI of the mean will also be provided, assuming a normal distribution. In case of departure from normality, results will be interpreted based on median and Interquartile Range (IQR).

Qualitative variables will be described using number of filled and missing data and, for each modality, the frequency and percentage (referring to filled data). A 95% confidence interval (CI) will be associated to binomial proportions using the Wilson score method.

Factors associated to an outcome of interest (ATTR vs other and ATTRwt vs ATTRv within patients diagnosed with ATTR-CM) will be identified using univariate logistic regression models. A separate logistic regression model will be created for each factor (as well as covariates described in section 6.4). If the variable is significantly associated to the outcome at the 10% level then the factor will be put forward into a multivariate model. Once the univariate model selection is complete, backwards selection will be used to remove factors from the multivariate model which do not have a significant p value at the 5% level. The covariate with the highest p value will be removed in turn until all factors have a p value less than 0.05. If a significant interaction is found then the individual factors of this interaction will be kept in the model, regardless of their p value. A significant interaction is tested for between all variables in the multivariate model.

Furthermore, a table showing all of the 95% confidence intervals and p values for the odds ratios coming from the univariate and multivariate models will be created.

8.2 STATISTICAL ANALYSES

Analyses will be provided overall and by subgroup defined in section 5.3.

Safety analyses

The safety analysis will be performed on the SAF population. AEs will be listed based on data recorded in the eCRF. A flag will be added to the AEs listing to identify patients who meet eligibility (inclusion/exclusion) criteria and with a radionuclide bone scintigraphy and/or SPECT performed with ^{99m}Tc-DPD/^{99m}Tc-PYP/^{99m}Tc-HMDP. No statistical test will be performed.

Analysis of primary and secondary objectives

For each objective, a percentage/prevalence with its 95%CI will be assessed overall and in the sub-groups defined in section 5.3 if pertinent.

Endpoints	**Population or Subgroup**
Percentage of patients with cardiac fixation at the radionuclide bone scintigraphy and/or SPECT performed with ^{99m}Tc-DPD or ^{99m}Tc-PYP or ^{99m}Tc-HMDP among patients with (left ventricular hypertrophy) LVH from an undiagnosed etiology	FAS1
Prevalence of Transthyretin amyloid (ATTR) or patients with suspicion of MGUS / AL amyloidosis	FAS1
Prevalence of hereditary (ATTRv) and wild-type (ATTRwt) ATTR amyloidosis in patients with positive scintigraphy	FAS2 & 3 (including 3.1 and 3.2)
Prevalence of TTR genetic mutation in patients with positive scintigraphy	FAS2 & 3 (including 3.1 and 3.2)
Prevalence of patients with familial history of known cardiomyopathy (CM), polyneuropathy (PN), sudden cardiac death (SCD) among their relatives (parents, siblings and 2nd /3rd grade family)	FAS1, 2 & 3 (including 3.1, 3.1(ATTRv), 3.1(ATTRwt) and 3.2)
Prevalence of patients with Senso-motor Polyneuropathy	FAS2 & 3 (including 3.1, 3.1(ATTRv), 3.1(ATTRwt) and 3.2)

Endpoints	**Population or Subgroup**
Prevalence of patients with CTS	FAS2 & 3 (including 3.1, 3.1(ATTRv), 3.1(ATTRwt) and 3.2)
Prevalence of patients with autonomic dysfunction	FAS2 & 3 (including 3.1, 3.1(ATTRv), 3.1(ATTRwt) and 3.2)
Prevalence of patients with cardiological manifestations	FAS2 & 3 (including 3.1, 3.1(ATTRv), 3.1(ATTRwt) and 3.2)
Prevalence of patients with laboratory signs	FAS2 & 3 (including 3.1, 3.1(ATTRv), 3.1(ATTRwt) and 3.2)
Description of the clinical and biochemical characteristics between patients with positive scintigraphy (cardiac fixation at the bone scintigraphy grade 1, 2 or 3) and/or SPECT (See section 0 § 3).	FAS2 & 3 (including 3.1, 3.1(ATTRv), 3.1(ATTRwt) and 3.2)
Discrepancy in the evaluation of the scintigraphy and/or SPECT images by different evaluators (See section 0 § 7)	FAS1

Other analyses

1. Patient characteristics

A full description of patient characteritics will be provided in the FAS1.

2. Analysis of redflags

The prevalence of each redflag will be assessed in the FAS 1, 2 & 3 population.

3. Description of variables of interest

Variables of interest are all variables collected in the CRF (including Kappa, Lambda, IgG, IgA and IgM rates from monoclonal protein studies).

- Variables of interest will be described in the FAS2 & 3 population in patients with 1, 2 or 3 redflags.
- Variables of interest will be described in the FAS1 population in patients with grade 0/1/2/3.
- Variables of interest will be described in the FAS2 & 3 population in patients with ATTRv and ATTRwt.

4. Comparaison between patients with final diagnosis of ATTR-CM and screened patients

Patients with a final diagnosis of ATTR-CM will be compared with the other "negative" screened patients in order to highlight possible diagnostic TTR-Amyolosis red flags

5. Factors associated to positive scintigraphy

Factors associated to positive scintigraphy will be identified in the FAS1 by univariate and multivariate logistic regression. This analysis will be performed in the FAS1 population and will include all variables collected in the CRF for both positive and negative scintigraphy. Clinical laboratories will be excluded from this analysis as only available for positive scintigraphy.

6. Factors associated to grade 2-3 scintigraphy and ATTR-CM

Factors associated to grade 2 or 3 will be identified in the FAS1 by univariate and multivariate logistic regression (compared with negative patients). This analysis will be performed in the FAS1 population and will include all variables collected in the CRF for both positive and negative scintigraphy. Clinical laboratories will be excluded from this analysis as only available for positive scintigraphy. The same analysis will be repeated to identify factors associated to ATTR-CM (FAS 2 & 3).

7. Scintigraphy discrepancies analysis

Discrepancy in the evaluation of the scintigraphy and/or SPECT images by different evaluators will be analyzed as follow:

- Between site and 1st evaluator:
  Cross tabulation between the two evaluators

Scintigraphy or SPECT images	Site evaluation				
1st external evaluator	Grade	0	1	2	3
	0				
	1				
	2				
	3				

All percentages of discrepancies will be provided.
A weighted Kappa coefficient (measure of interrater agreement) will be provided with 95% confidence limits and exact test for the kappa coefficient.

- Between 1st and 2nd evaluators (in case there is a discrepancy between site evaluation and 1st external evaluator), same analyses will be performed.

- A listing of all individual patients will be provided for all discrepancies (site and the 2 external evaluations).

8. Sensitivity analyses

1) Impact of protocol amendment 2 - Use of SPECT
The prevalence of patients with cardiac fixation at the radionuclide bone scintigraphy and/or Single Photon Emission Computed Tomography (SPECT) performed with 99mTc-DPD or 99mTc-PYP or 99mTc-HMDP* among patients with (left ventricular hypertrophy) LVH from undiagnosed etiology will be calculated in patients included before protocol amendement and in patients included after protocol amendement (Amendement 2 – Date: 11-Feb-2020). The percentage and its 95% CI will be provided.

2) Impact of protocol amendment 2 – No longer using a centralized lab
The prevalence of patients with laboratory signs will be calculated in patients included before protocol amendement and in patients included after protocol amendement (Amendement 2 – Date: 11-Feb-2020). The percentage and its 95% CI will be provided.

9 LIST OF TABLES AND TABLE SHELLS

A list of tables will be provided in a separate document. An example of some table shells is presented below:

Table 15.1.1 Number and Percentage of Patients in Each Analysis Set

Analysis Set		Grade 0 (N=XX)	Grade 1 (N=XX)	Grade 2 (N=XX)	Grade 3 (N=XX)	Unknown grade (N=XX)	Total (N=XX)
Selected	No						xx (xx.x%)
	Yes						xx (xx.x%)
FAS1	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
FAS2	No		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
FAS3	No		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
FAS4	No		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Safety Set	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

…

Table 15.1.2 Demography and Baseline Characteristics – FAS1, 2

Variables		Grade 0	FAS 2				Total (FAS 1)
			Grade 1	Grade 2	Grade 3	Grade 1 or 2 or 3	
		(N=XX)	(N=XX)	(N=XX)	(N=XX)	(N=XX)	
Age (years)	N	xx	xx	xx	xx	xx	xx
	Mean ± SD	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min. ; Max.	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx
	Missing	x	x	x	x	x	x
Age (in class)	[50 - 55] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	]55 - 60] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	]60 - 65] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	]65 - 70] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	]70 - 75] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	]75 - 80] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	over 80 years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gender	Missing	xx	xx	xx	xx	xx	xx
	Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Weight (kg)	N	xx	xx	xx	xx	xx	xx
	Mean ± SD	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min. ; Max.	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx
	Missing	x	x	x	x	x	x
BMI (kg/m²)	N	xx	xx	xx	xx	xx	xx
	Mean ± SD	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min. ; Max.	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx
	Missing	x	x	x	x	x	x

…

Table 15.1.2 Demography and Baseline Characteristics – FAS 2&3

Variables		Grade 1	FAS 3					Total (=FAS 2)
			ATTRwt	ATTRv	ATTR (=FAS 3.1)	FAS 3.2	All FAS 3	
		(N=XX)	(N=XX)	(N=XX)	(N=XX)	(N=XX)	(N=XX)	
Age (years)	N	xx	xx	xx	xx	xx	xx	xx
	Mean ± SD	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min. ; Max.	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx
	Missing	x	x	x	x	x	x	x
Age (in class)	[50 - 55] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	]55 - 60] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	]60 - 65] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	]65 - 70] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	]70 - 75] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	]75 - 80] years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	over 80 years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gender	Missing	xx	xx	xx	xx	xx	xx	xx
	Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Weight (kg)	N	xx	xx	xx	xx	xx	xx	xx
	Mean ± SD	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min. ; Max.	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx
	Missing	x	x	x	x	x	x	x
BMI (kg/m²)	N	xx	xx	xx	xx	xx	xx	xx
	Mean ± SD	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min. ; Max.	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx	xx ; xx
	Missing	x	x	x	x	x	x	x

…

…

Table 15.2.1 Prevalence of Patients with Cardiac Fixation at the Radionuclide Bone Scintigraphy and / or SPECT Performed – FAS1

Variable(s)		Total (N=XX)
Prevalence of patients with cardiac fixation at the radionuclide bone scintigraphy and /or SPECT performed		xx (xx.x%)
	IC95%	[xx.x% - xx.x%]

...

Table 15.2.2 Factors Associated to Positive Scintigraphy (Logistic Regression Model) – FAS1

	Positive Scintigraphy		Univariate Analysis		Multivariate Analysis	
Explanatory Variable	Yes (N=xx)	No (N=xx)	Odds-Ratio [95% CI]	p-value	Odds-Ratio [95% CI]	p-value
n	xx	xx				
Missing data	x	x				
Factor 1 (qualitative)				x.xxx		x.xxx
Modality 1 (reference)	xx (xx.x%)	xx (xx.x%)	1.00		1.00	
Modality 2	xx (xx.x%)	xx (xx.x%)	x.xx [x.xx;x.xx]		x.xx [x.xx;x.xx]	
Factor 2 (quantitative)				x.xxx		x.xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)				
Per XX-unit increment			x.xx [x.xx;x.xx]		x.xx [x.xx;x.xx]	

10 REFERENCES

NA

11 APPENDICES

11.1 APPENDIX 1: DATA DERIVATION DETAILS

Age = (Patient screening visit date – Birthdate + 1) /365.25 , where day of birth is imputed to 15, as only month and year of birth are recorded.

Diastolic Blood Pressure classes:

- < 60 mmHg,
- [61 – 70] mmHg,
- [71 – 80] mmHg,
- [81 – 90] mmHg,
- [91 – 100] mmHg,
- > 100 mmHg.

Heart Rate classes:

- < 50 bpm,
- [51 – 60] bpm,
- [61 – 70] bpm,
- [71 – 80] bpm,
- [81 – 90] bpm,
- [91 – 100] bpm,
- [101 – 120] bpm,
- > 120 bpm.

PR interval classes:

- [90 – 100] ms
- [101 – 110] ms
- [111 – 120] ms
- [121 – 130] ms
- [131 – 140] ms
- [141 – 150] ms
- [151 – 160] ms
- [161 – 170] ms
- [171 – 180] ms
- [181 – 190] ms
- [191 – 200] ms
- [201 – 210] ms
- [211 – 220] ms
- [221 – 230] ms

- [231 – 240] ms
- [241 – 250] ms
- [251 – 260] ms
- [261 – 270] ms
- [271 – 280] ms
- > 280 ms

Serum Free Light Chain Ratio:
sFLC Ratio = Kappa / Lambda,

sFLC ratio classes:
- < 0.26,
- [0.26 – 1.65],
- > 1.65.

Abormal values for all quantitative variables will be defined after medical advise.