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Brief lay title:	EMP-Activity
SEAP version identifier:	*1.0*
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TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
BI	Boehringer Ingelheim
CRF	Case report form
CSS	Clinical summary score (KCCQ)
DM	Diabetes mellitus
DMRP	Data management and review plan
FAS	Full analysis set
HF	Heart Failure
ICH	International conference on harmonisation
KCCQ	Kansas City Cardiomyopathy Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-interventional study
NISnd	NIS with newly collected data
NYHA	New York Heart Association
OSS	Overall summary score (KCCQ)
PT	MedDRA Preferred term
RWE	Real world evaluation
RWE COE	Real world evaluation center of excellence
SAE	Serious adverse event
SEAP	Statistical and epidemiological analysis plan
SmPC	Summary of product characteristics
SOC	MedDRA System organ class
SOP	Standard operating procedure
TDM	Trial data manager
TLF	Tables, lists and figures
TM Epi	Team Member Epidemiology
TSS	Total symptom score (KCCQ)
TSTAT	Trial statistician

2. RESPONSIBLE PARTIES

NIS Statistician [SEAP author]

- [redacted] Statistician)

SEAP reviewers are:

- BI NIS [redacted] [SEAP reviewer] (in all cases)
  - [redacted]
- NIS Data [redacted] [SEAP reviewer] (in all cases)
  - [redacted]
- RWE CoE [SEAP reviewer]
  - [redacted]
- TSTAT
  - [redacted]
- TM Epi [SEAP reviewer] (When BI NIS lead is not TM Epi; in all cases)
  - [redacted]

3. PURPOSE AND SCOPE

As per ICH E9 [1] (International Conference on Harmonisation), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Statistical and Epidemiological Analysis Plan (SEAP) assumes familiarity with the Observational plan, including Protocol Amendments. In particular, the SEAP is based on the planned analysis specification as written in Observational plan Section 9.7 “Data Analysis”. Therefore, SEAP readers may consult the Observational plan for more background information on the study, e.g., on study objectives, study design and population, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.4 (or later version) will be used for all standard analyses.

4. AMENDMENTS AND UPDATES

None.

5. RESEARCH QUESTION AND OBJECTIVE

5.1 PRIMARY OBJECTIVE

The primary objective of this observational study is to describe the change of the clinical summary score (CSS), total symptom score (TSS), and overall summary score (OSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) from baseline to 24 weeks in patients with chronic HF newly treated with empagliflozin according to routine practice.

5.2 SECONDARY OBJECTIVE

To describe the change of the New York Heart Association (NYHA) Class from baseline to 24 weeks in patients with chronic HF newly treated with empagliflozin.
To capture real-world patterns of patient characteristics and clinical disease presentation according to therapeutic regimen chosen in participants with chronic HF

5.3 ADDITIONAL OBJECTIVE

None

6. RESEARCH METHODS

6.1 STUDY DESIGN

This is a multinational non-interventional study based on newly collected data (NISnd) to assess demographics, and treatment pattern of patients with HF in a two-cohort design: one cohort with first prescription of empagliflozin as routine therapy for HF, the other cohort with an alternative non-SLGT2i treatment for HF. Treatment of HF according to routine practice is determined by the physician independent of the participation of the patient in this non-interventional study.
For more details on study design please see section 9.1 of the Study Protocol.

6.2 SETTING

In this NISnd, data from a total of about 4600 HF patients will be collected during routine clinical practice by private practice and clinics in 8 countries (Poland, Romania, Hungary, Switzerland, Czech Republic, Bulgaria, Slovenia, and Serbia).
There will be no procedure outside routine clinical practice except for handing out the KCCQs to the enrolled patients by the study staff. The physician's decision to initiate treatment with empagliflozin or a non-SGLT2i HF drug is independent of the registration of the patient in this study. A patients with documented baseline evaluation is considered enrolled.
This study is planned to observe patients treated with empagliflozin for approximately 24 weeks, whereas data of the comparison group are collected at visit 1 exclusively. In addition to data collected by the physician, all patients should fill in the KCCQ-questionnaire at visit 1, whereas only patients receiving empagliflozin must fill in the questionnaire after approximately 24 weeks to address the change in disease specific symptoms and items

regarding physical functioning and self-care during empagliflozin therapy in a real-world patient population.

6.3 STUDY POPULATION

Indication

Patients to be recruited within this study must have a physician diagnosed symptomatic chronic HF for which empagliflozin is an indicated treatment. Diabetic patients as well as non-diabetic patients can be enrolled.

Patients fulfilling the following eligibility criteria will be enrolled into the empagliflozin (cohort A) or the non-SGLT2i arm (cohort B) according to the physician's choice of HF treatment.

Inclusion criteria

Patients can be included if all of the following criteria are met:

- Written informed consent prior to study participation
- Male and female patients ≥ 18 years at Visit 1
- Patients must be contractually capable and mentally able to understand and follow the instructions of the study personnel
- Hospitalized patients with diagnosis of chronic heart failure NYHA Class II-IV at Visit 1
- Treatment-naïve for SGLT2i at visit 1 (no pretreatment with SGLT2i ever)
- Women of childbearing potential must take appropriate precautions against getting pregnant according to approval of chosen HF drug(s)

Exclusion criteria

Patients cannot be included if any of the following criteria is met:

- Life expectancy ≤12 months according to physician's assessment
- Pregnant or lactating females
- Participation in a parallel interventional clinical trial
- Chosen treatment with another SGLT2i drug than empagliflozin
- Prior treatment with SGLT2i at visit 1
- Patients with contraindications according to current SmPC
- Patients with dependency or relationship to the treating physician•Patients with prior history of ketoacidosis
- Patient with type1 DM

6.4 STUDY VISITS

All patients will have baseline visit (visit 1) on the day of prescription of empagliflozin (cohort A) or non-SLGT2i (cohort B).
Primary goal of this NIS is to describe the change of the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores [clinical summary score (CSS), total symptom score (TSS), overall summary score (OSS)] from baseline to 24 weeks in patients newly treated with empagliflozin according to routine practice. Therefore, a visit 2 at week 24 (±2 weeks) is implemented in cohort A.
The patients have the right to stop study participation any time and for any reason, without any drawback on their further treatment
For more details on study visits please see section 9.2.3 of the Study Protocol.

7. VARIABLES

The following parameters will be collected at **visit 1** (= index date 1) of all registered patients:

1. Patient demographics:
   - Year of birth
   - Gender
   - Height, weight, BMI (will be calculated from height and weight)
2. Date of first diagnosis of HF
3. Etiology of heart failure
   - Coronary artery disease
   - Hypertension
   - Valve disease
   - Cardiomyopathy
   - Congenital heart disease
   - Drug induced
   - Infective
   - Storage disorders
   - Diabetes
   - Obesity
   - Other
4. Clinical parameters relevant for HF (last available value and date when it was collected) as valid at baseline and performed during clinical routine:
   - LVEF [%]
   - Current NYHA Class [I-IV] according to treating physician
   - Electrocardiogram (ECG) (normal/abnormal-not clinically significant/abnormal-clinical significant and QTc interval)
   - Heart rate [bpm]
   - Blood pressure (systolic, diastolic) [mmHg]
   - Laboratory diagnostic according to clinical routine (last available value and date when it was collected):
     - BNP (B-type natriuretic peptide) and/or pro-BNP (N-terminal pro–B-type natriuretic peptide)
     - Lipids (cholesterol, HDL, LDL)
     - Blood urea nitrogen (BUN)
     - Serum creatinine
     - Sodium, potassium
     - Complete blood count
   - 6-min-walking test according to clinical routine
5. Alcohol consumption (none, from time to time, regular) and smoking status (non-smoker, previous smoker, current smoker)
6. Concomitant diseases / Comorbidities
   - Disease according to ICD-10 (diabetes, hypertension, coronary artery

disease, infarction, chronic kidney disease, atrial fibrillation, cancer, other)
- Date of first diagnosis

7. Previous HF hospitalizations within the last 6 months
8. HF related medication used in the last 6 months
   - Medication
   - Indication
   - Application
   - Dose
   - Start date, end date, continuing
9. Current HF related and other relevant concomitant medication
   - Medication
   - Indication
   - Application
   - Dose
   - Start date, end date, continuing
10. Newly prescribed treatment regime:
    - Date of prescription
    - Medication (empagliflozin and / or other drug)
    - Reason, if no prescription of empagliflozin
11. Patient reported outcomes:
    - KCCQ (23 items) completed by patients during the visit

The following parameters will be collected at routine **visit 2** [= index date 2: 24 weeks (±2 weeks) after index date 1] only of registered patients treated with empagliflozin:

1. Weight, BMI (will be calculated from height and weight)
2. Clinical parameters relevant for HF performed during clinical routine (last available value and date when it was collected):
   - LVEF
   - Current NYHA Class according to treating physician
   - Electrocardiogram (ECG)
   - Heart rate
   - Blood pressure (systolic, diastolic)
   - Laboratory diagnostic according to clinical routine (last available value and date when it was collected):
     - BNP (B-type natriuretic peptide) and/or pro-BNP (N-terminal pro–B-type natriuretic peptide)
     - Lipids (cholesterol, HDL, LDL)
     - Blood urea nitrogen (BUN)
     - Serum creatinine
     - Sodium, potassium
     - Complete blood count

- 6-min-walking test according to clinical routine

3. Current HF related or other relevant concomitant medication
4. HF drug(s) prescribed at visit 2
5. Patient reported outcomes:
   - KCCQ (23 items) completed by patients during the visit
6. Safety: ADRs (serious and non-serious), fatal adverse events (AEs), pregnancies, HF related hospitalizations
7. Discontinuation of treatment with empagliflozin during study period (yes/no)
   - If yes: date of discontinuation, reason (if applicable)
8. Continuation or discontinuation of treatment with empagliflozin after study period (yes/no)
   - In case of discontinuation: date of discontinuation, reason (if applicable)

The following variables have to be calculated:
BMI: Body weight [kg] / (Height [m])²

Kansas City Cardiomyopathy Questionnaire (KCCQ-23):
The Kansas City Cardiomyopathy Questionnaire Scoring Instructions
There are 10 summary scores within the KCCQ, which are calculated as follows:
1. Physical Limitation
• Code responses to each of Questions 1a-f as follows:
Extremely limited = 1
Quite a bit limited = 2
Moderately limited = 3
Slightly limited = 4
Not at all limited = 5
Limited for other reasons or did not do = <*missing value*>
• If at least three of Questions 1a-f are not missing, then compute
Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4
(see footnote at end of this section for explanation of meaning of "actually answered")
2. Symptom Stability
• Code the response to Question 2 as follows:
Much worse = 1
Slightly worse = 2
Not changed = 3
Slightly better = 4
Much better = 5
I've had no symptoms over the last 2 weeks = 3
• If Question 2 is not missing, then compute
Symptom Stability Score = 100*[(Question 2) – 1]/4
3. Symptom Frequency
• Code responses to Questions 3, 5, 7 and 9 as follows:

Question 3

Every morning = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

Questions 5 and 7

All of the time = 1
Several times a day = 2
At least once a day = 3
3 or mo re times a week but not every day = 4
1-2 times a week = 5
Less than once a week = 6
Never over the past 2 weeks = 7

Question 9

Every night = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

• If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

S3 = [(Question 3) – 1]/4
S5 = [(Question 5) – 1]/6
S7 = [(Question 7) – 1]/6
S9 = [(Question 9) – 1]/4

Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

• Code responses to each of Questions 4, 6 and 8 as follows:

Extremely bothersome = 1
Quite a bit bothersome = 2
Moderately bothersome = 3
Slightly bothersome = 4
Not at all bothersome = 5
I've had no swelling/fatigue/shortness of breath = 5

• If at least one of Questions 4, 6 and 8 is not missing, then compute

Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

= mean of the following available summary scores:
Symptom Frequency Score
Symptom Burden Score

6. Self-Efficacy

• Code responses to Questions 10 and 11 as follows:

Question 10

Not at all sure = 1
Not very sure = 2

Somewhat sure = 3
Mostly sure = 4
Completely sure = 5

Question 11

Do not understand at all = 1
Do not understand very well = 2
Somewhat understand = 3
Mostly understand = 4
Completely understand = 5

• If at least one of Questions 10 and 11 is not missing, then compute

Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

• Code responses to Questions 12, 13 and 14 as follows:

Question 12

It has extremely limited my enjoyment of life = 1
It has limited my enjoyment of life quite a bit = 2
It has moderately limited my enjoyment of life = 3
It has slightly limited my enjoyment of life = 4
It has not limited my enjoyment of life at all = 5

Question 13

Not at all satisfied = 1
Mostly dissatisfied = 2
Somewhat satisfied = 3
Mostly satisfied = 4
Completely satisfied = 5

Question 14

I felt that way all of the time = 1
I felt that way most of the time = 2
I occasionally felt that way = 3
I rarely felt that way = 4
I never felt that way = 5

• If at least one of Questions 12, 13 and 14 is not missing, then compute

Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

• Code responses to each of Questions 15a-d as follows:

Severely limited = 1
Limited quite a bit = 2
Moderately limited = 3
Slightly limited = 4
Did not limit at all = 5
Does not apply or did not do for other reasons = <*missing value*>

• If at least two of Questions 15a-d are not missing, then compute

Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

= mean of the following available summary scores:

Physical Limitation Score
Total Symptom Score
Quality of Life Score
Social Limitation Score

10. Clinical Summary Score
= mean of the following available summary scores:
Physical Limitation Score
Total Symptom Score

Footnote: references to "**means of questions actually answered**" imply the following.
If there are *n* questions in a scale, and the subject must answer *m* to score the scale, but the subject
answers only *n-i*, where *n-i* >= *m*, calculate the **mean of those questions** as
(sum of the responses to those *n-i* questions) / (*n-i*)
not
(sum of the responses to those *n-i* questions) / *n*

Left ventricular ejection fraction (LVEF): HF can be classified into 3 subtypes with different underlying aetiologies:

1. HF with reduced ejection fraction (HFrEF) (LVEF $\leqslant$ 40%),
2. HF with preserved ejection fraction (HFpEF) (LVEF $\geqslant$ 50%) and
3. HF with mildly reduced LV systolic function (HFmrEF) (LVEF = 41-49%).

Time to discontinuation of empagliflozin treatment: Time to discontinuation of empagliflozin treatment will be analyzed descriptive using Kaplan-Meier methods. For patients who discontinued empagliflozin treatment it will be derived as date of end of treatment - date of start of treatment +1, patients still on treatment will be censored with date of last contact.

7.1 EXPOSURES

The drug of interest is Jardiance® with the active ingredient empagliflozin. Within this study, there are two HF patient cohorts: patients receiving first prescription of empagliflozin and those who have been prescribed a drug with a different mechanism of action for the treatment of HF, i.e. non-SGLT2i.
During this study, it is planned to observe for each patient who receives a first prescription of empagliflozin a treatment period of approximately 24 weeks. Patients not treated with empagliflozin will not be observed further after visit 1.
The recommended daily dose of empagliflozin for treatment of heart failure is 10 mg once daily.

7.2 OUTCOMES

7.2.1 Primary outcomes

Change of the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores [clinical summary score (CSS), total symptom score (TSS), overall summary score (OSS)] from index date 1

(baseline) to index date 2 (24 weeks after index date 1) in patients newly treated with empagliflozin according to routine practice.

7.2.2 Secondary outcomes

- Change of the New York Heart Association (NYHA) Class from index date 1 to index date 2 (24 weeks after index date 1) in patients newly treated with empagliflozin.
- Real-world patterns of patient characteristics, clinical disease presentation and therapeutic regimen chosen in participants with chronic HF as well as of patient reported outcome at visit 1.

[redacted]

7.3 COVARIATES

Demographics and disease characteristics will be used to define subgroups of interest.

8. DATA SOURCES

Medical records collected through routine clinical care will be used to assess the inclusion/exclusion criteria of patients as well as for patient demographics, current HF medication, concomitant diseases, and concomitant medication, as well as for the health data of the patient at visit 2.
The KCCQ will be provided as paper version by the treating physician or trained site stuff to the patient to be filled out in writing at visit 1 (all patients) and visit 2 (patients with initial empagliflozin treatment only).

9. DATA MANAGEMENT AND SOFTWARE / TOOLS

9.1 SOFTWARE/TOOLS

SAS® Version 9.4 or higher will be used for all analyses.

9.2 HANDLING OF MISSING VALUES

All patient discontinuations will be documented and the reason for discontinuation will be recorded.
In general, it is not planned to impute missing values. Exceptions are detailed in the subsequent subsections.

9.3 HANDLING OF INCONSISTENCIES IN DATA AND OUTLIERS

Not planned.

10. DATA ANALYSIS

Full analysis set (FAS): All registered patients who gave informed consent.
All data captured at visit 1 will be analysed for FAS.
Primary endpoint set (PES): All patients, who received at least one dose of empagliflozin for HF and have filled in KCCQ at time points index date 1 and 24 week follow-up visit.
The primary endpoint will be analysed for PES.
Safety set (SAF): All patients of FAS who received empagliflozin at least once.
SAF will be used for safety and further analyses.

For continuous variables number of values, mean, standard deviation, minimum, 5th percentile, 25th percentile, median 75th percentile, 95th percentile, maximum and number of missing values will be presented. For categorical variables the number and percentage with a category for missing will be given.
Percentages will be rounded to two decimal places.

10.1 MAIN ANALYSIS

Analysis of the primary outcome

- Change of each of the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores [clinical summary score (CSS), total symptom score (TSS), overall summary score (OSS)] from index date 1 to index date 2 (= 24 weeks after index date 1) in patients newly treated with empagliflozin according to routine practice

will be performed according to the analysis manual for the KCCQ. Changes in the KCCQ scores will be calculated for each patient. Results will be presented as N, mean, standard deviation, median, minimum and maximum values as well as number of missings as extra column. A change of 5 points of OSS will be considered as clinically meaningful.
In addition, change from index date 1 in clinical summary score for HF symptoms and physical limitations domains of the KCCQ at week 24 will be evaluated by subgroups based on age at index date 1(<50/50-<65/65-<75/≥75 years as well as <65/≥65 years), gender, country, baseline LVEF (HFrEF, HFmrEF HFpEF), and status of diabetes mellitus at visit 1.
All recorded data for efficacy up to week 24 will be included.

For analysis of the secondary outcome

- Change of the New York Heart Association (NYHA) Class from index date 1 to index date 2 (= 24 weeks after index date 1) in patients newly treated with empagliflozin

tabulation of relative and absolute frequencies will be presented as well as a shift table.

For the analysis of the secondary outcome

- Capture of real-world patterns of patient characteristics, clinical disease presentation and therapeutic regimen chosen in participants with chronic HF as well as of patient reported outcome at visit 1

tabulations of relative and absolute frequencies will be presented. Comparison of data at visit 1 between patients receiving empagliflozin or not for treatment of HF will be performed by Chi- quadrat-test or Mann-Whitney-U-test or Student t-Test.

[redacted]

10.3 SAFETY ANALYSIS

All adverse drug reactions (ADRs) (serious and non-serious), all AEs with fatal outcome, hospitalizations due to HF as collected per study protocol will be included and summarized in the final study report.
Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. In general, safety analyses will be descriptive in nature.
Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. All adverse events occurring after start of empagliflozin treatment and up to 7 days after last empagliflozin treatment will be considered 'treatment-emergent'. Deterioration of pre-existing conditions will also be considered 'treatment- emergent'.
Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA. Furthermore, the worst outcome per patient will be presented as well as reason for seriousness.
In addition frequency of non treatment-emergent AE will be given by SOC and PT.

11. QUALITY CONTROL

To ensure correct analysis conduct and implementation following [redacted] SOPs will be considered:

- Checklist for FormFake acceptance (SLC03-A09)
- Preparation of Statistical Analysis Plan (SAP) on the basis of protocol and CRF and review (SA02-A02)
- Generation of SAS programs for statistical analyses on the basis of given specifications/SAP (SA03)
- Quality Assurance of SAS programming, code review, cross-output check of SAS programs (SA04-V06)
- Verifying of statistical output, cross-output check (SA04-A01, A03, A07)
- SAS log file provides traceability of the several steps of analysis
- Preparation of the Table, List and Figures (TLFs) (SA05)

12. REFERENCES

12.1 PUBLISHED REFERENCES

[1] CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.

12.2 UNPUBLISHED REFERENCES

None.

ANNEX 1. ADDITIONAL INFORMATION

The shell of the tables, figueres and listings will be provided as a separate document..

ANNEX 2. REVIEWERS AND APPROVAL SIGNATURES

The NIS SEAP must be sent for review to the following individuals **prior to approval**.

Reviewer	**NIS involving BI product(s)**	**NIS not involving BI product(s)**	
		Global NIS	**Local NIS**
NIS Lead	X	X	X
Global TM Epi*	X	X	X
NIS Data Manager	X	X	X
TSTAT (for NISnd only)	X	X	X
RWE CoE	X	X	

** When BI NIS lead is not TM Epi*

Study Title: **NIS EMP-Activity**

Study Number: 1245-0259

Protocol Version: EMP-Activity_Observational Plan_version-03_30-Sept-2022

I herewith certify that I agree to the content of the study SEAP and to all documents referenced in the study SEAP.

Position: NIS [redacted]	Name: [redacted] Date:	Signature:
Position: TM BDS	Name: [redacted] Date:	Signature:
Position: NIS Data [redacted]	Name: [redacted] Date:	Signature:
Position: Trial Statistician	Name: [redacted] Date:	Signature:
Position: RWE CoE	Name [redacted] Date:	Signature:

13. HISTORY TABLE

Table 1: History table

Version	Date	Author	Sections changed	Brief description of change
Draft v0.1		[redacted]	None	This is the first Draft-Version of SEAP without any modification.
Draft v0.2	24 Feb 2023		1, 2, 6.1, 6.2, 7, 8, 10, 10.1, 10.2, Annex 2	Minor changes and additions Responsible parties (BI)
Final 1.0	02 Nov 2023		1, 6.1, 6.2, 6.3, 6.4,7, 7.1, 7.3, 10 and Annex 2	Minor changes and additions Responsible parties (BI)

APPROVAL / SIGNATURE PAGE

Document Number: c42980073 **Technical Version Number:1.0**

Document Name: 08-01-tsap

Title: Empagliflozin functional capacity - Non-Interventional Study

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval	[redacted]	02 Nov 2023 13:32 CET
Approval-Data [redacted]		02 Nov 2023 14:14 CET
Approval-Biostatistics		08 Nov 2023 08:46 CET
Approval		24 Nov 2023 09:33 CET
Approval-Biostatistics		24 Nov 2023 10:24 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**