Cover page for Protocol and Statistical Analysis Plan

Sponsor name	Ferring Pharmaceuticals A/S
NCT Number	NCT04740645
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Official title of study	Post-authorisation safety study of NOCDURNA for the symptomatic treatment of nocturia due to idiopathic nocturnal polyuria: A multi-country cohort study using secondary data
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POST AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

Post-authorisation safety study of NOCDURNA for the symptomatic treatment of nocturia due to idiopathic nocturnal polyuria: A multi-country cohort study using secondary data

COMPOUND: Desmopressin

STUDY NUMBER: 000248

Name and Address of Sponsor: Ferring Pharmaceuticals A/S
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Version Number:	3.0		
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PASS Information

Title	Post-authorisation safety study of NOCDURNA for the symptomatic treatment of nocturia due to idiopathic nocturnal polyuria: A multi-country cohort study using secondary data
Protocol version identifier	V 3.0
Date of last version of protocol	10 Nov 2020
EU PAS register number	To be registered
Active substance	Desmopressin, ATC code: H01BA02
Medicinal product	NOCDURNA 25/50 micrograms oral lyophilisate
Product reference	N/A
Procedure number	SE/H/1507/01-02/DC
Marketing authorization holder(s)	Denmark: Ferring Lægemidler A/S Kay Fiskers Plads 11 DK-2300 Copenhagen S, Denmark Germany: Ferring Arzneimittel GMBH Fabrikstrasse 7 24103 Kiel, Germany Sweden: Ferring Läkemedel AB Box 4041 203 11 Malmö, Sweden
Joint PASS	NO
Research question and objectives	This is a retrospective study to assess the post-authorisation safety of NOCDURNA using longitudinal real-world data. In addition, since it is desirable to put these observations into context and characterise a population with similar indications who do not receive desmopressin, a similar number of patients receiving standard care for other lower urinary tract symptoms (LUTS) will be evaluated in order to inform on the safety and utilisation of NOCDURNA Primary objective: • To estimate the incidence rate of symptomatic hyponatraemia (defined as a recorded diagnosis of hyponatraemia) among patients treated with NOCDURNA, and patients with LUTS separately, overall and by subgroups of interest (including elderly patients, aged ≥65 years). Secondary objectives: 1. To describe demographic and health characteristics of the population receiving NOCDURNA and patients with LUTS, including prevalence of risk factors for outcomes of interest.

	2. To estimate incidence rate of hyponatraemia requiring hospital intensive care among patients treated with NOCDURNA and patients with LUTS separately. 3. To estimate incidence rate of clinically significant hyponatraemia (defined as a serum sodium concentration of <130 mmol/L) among patients treated with NOCDURNA and patients with LUTS separately. 4. To estimate rate of all-cause mortality among patients treated with NOCDURNA and patients with LUTS separately. 5. To estimate incidence rate of the following events of special interest among patients treated with NOCDURNA and patients with LUTS separately: a. Major cardiovascular events (MACE, composite endpoint) b. Major venous thromboembolic events (VTE, composite endpoint) To estimate incidence rate of acute exacerbation of congestive heart failure among patients who have chronic cardiac insufficiency treated with NOCDURNA, and patients with LUTS, separately. 6. To estimate incidence rate of primary and secondary outcomes of interest between patients treated with NOCDURNA compared to a population of LUTS patients adjusted for confounding factors, by country where data available. 7. To estimate incidence rate of cardiovascular and thromboembolic events of interest resulting in treatment withdrawal of NOCDURNA 8. To estimate incidence rate in patients adhering to the label as assessed by the proxy based on diagnosis and contra-indication (as available) All secondary objectives will be evaluated in the overall population and among subgroups of interest (including elderly, aged ≥65 years).
Countries of study	Denmark, Germany and Sweden
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IQVIA is a partner of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), which is coordinated by the European Medicines Agency. IQVIA is dedicated to excellence in research by adhering to the ENCePP Guide on Methodological Standards and promoting scientific independence and transparency.

Marketing authorization holder(s)

Marketing authorization holder(s)	Denmark: Ferring Lægemidler A/S Kay Fiskers Plads 11 DK-2300 Copenhagen S, Denmark Germany: Ferring Arzneimittel GMBH Fabrikstrasse 7 24103 Kiel, Germany Sweden: Ferring Läkemedel AB Box 4041 203 11 Malmö, Sweden
Sponsor	Ferring Pharmaceuticals A/S Kay Fiskers Plads 11 DK-2300 Copenhagen S Denmark
Sponsor representative	To be determined

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ATC	Anatomic Therapeutic Chemical
BIPS	The Leibniz Institute for Prevention Research and Epidemiology
CI	Confidence interval
CPR	Central Person Registry
DA	Disease Analyzer
DCP	Decentralised procedure
DCRS	Danish Civil Registration System
DNPR	Danish National Patient Registry
DRCD	Danish Registry of Causes of Death
DRMPS	Danish Registry of Medicinal Products Statistics
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	European Union electronic Register of Post-Authorisation Studies
GEP	Good Epidemiological Practice
GePaRD	The German Pharmacoepidemiological Research Database
GPP	Good Pharmacoepidemiology Practice
GPS	Good Practice of Secondary Data Analysis
GVP	Good pharmacovigilance practices
ICD-10	International Classification of Diseases, 10th Revision
IRR	Incidence rate ratio
ISPE	International Society of Pharmacoepidemiology
LPD	Longitudinal population database
LUTS	Lower urinary tract symptoms
MACE	Major adverse cardiovascular events
MPA	Medical Products Agency
NBHW	National Board of Health and Welfare
PASS	Post-authorization safety study
PIN	Personal identity number
SAP	Statistical analysis plan
SCDR	Swedish Cause of Death Registry
SHI	Statutory Health Insurance
SIR	Swedish Intensive Care Registry
SmPC	Summary of product characteristics
SNPR	Swedish National Patient Registry
SPDR	Swedish Prescribed Drug Registry
STPR	Swedish Total Population Registry
STROBE	Strengthening the reporting of observational studies in epidemiology
THIN	The Health Improvement Network
VTE	Venous thromboembolism

3 RESPONSIBLE PARTIES

Sponsor:

Ferring Pharmaceuticals A/S, Kay Fiskers Plads 11, DK-2300 Copenhagen S, Denmark.

Subcontractor acting as contracted principal investigator:

(To be confirmed)

4 ABSTRACT

Title

Post-authorisation safety study of NOCDURNA for the symptomatic treatment of nocturia due to idiopathic nocturnal polyuria: A multi-country cohort study using secondary data.

Rationale and background

Nocturia is defined as a complaint that an individual has to wake at night one or more times to void where each micturition is preceded and followed by sleep. Nocturia can be due to many factors, such as an underlying medical condition. However, some people experience nocturia due to idiopathic nocturnal polyuria, which means that although their total 24-hour production may remain normal, they produce an excessive amount of urine at night.

In 2016, Ferring Pharmaceuticals A/S, hereafter referred to as Ferring, finalised a decentralised procedure (DCP) in the European Union (EU) leading to the approval of NOCDURNA (desmopressin, gender-specific low doses of 25 µg for women and 50 µg for men) for the symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults. Some safety concerns relating to NOCDURNA were defined during the EU DCP; risk of hyponatraemia (especially in elderly patients aged ≥65 years), a potential risk of thromboembolic events (only expected at doses much higher than approved for NOCDURNA), and a potential risk of acute exacerbation of congestive heart failure in patients with compensated cardiac insufficiency. These safety concerns were based on data from clinical trials in haemophilia (OCTOSTIM, high-dose trials, exposure in the magnitude 10-20 higher than for urological indications), post-marketing experience and general knowledge about pharmacodynamics and physiology.

Against this background, the DCP member states have required that a post-authorisation safety study (PASS) is included in the NOCDURNA risk management plan to evaluate safety concerns and to collect long-term data on patients aged ≥65 years treated with NOCDURNA according to the approved summary of product characteristics.

Research question and objectives

Primary objective:

To estimate the incidence rate of symptomatic hyponatraemia (defined as a recorded diagnosis of hyponatraemia) among patients treated with NOCDURNA, and patients with lower urinary tract symptoms (LUTS) separately, overall and by subgroups of interest (including elderly patients, aged ≥65 years).

Secondary objectives:

The secondary objectives are to:

1. Describe the demographic and health characteristics of the population receiving NOCDURNA and patients with LUTS, including prevalence of risk factors for outcomes of interest.

2. Estimate the incidence rate of hyponatraemia requiring hospital intensive care among patients treated with NOCDURNA and patients with LUTS separately.

3. Estimate the incidence rate of clinically significant hyponatraemia (defined as a serum sodium concentration of <130 mmol/L) among patients treated with NOCDURNA and patients with LUTS separately.

4. Estimate the rate of all-cause mortality among patients treated with NOCDURNA and patients with LUTS separately.

5. Estimate the incidence rate of the following events of special interest among patients treated with NOCDURNA and patients with LUTS separately:
    a. Major adverse cardiovascular events (MACE, composite endpoint)
    b. Major venous thromboembolic events (VTE, composite endpoint)

    Estimate the incidence rate of acute exacerbation of congestive heart failure among patients who have chronic cardiac insufficiency treated with NOCDURNA, and patients with LUTS, separately. In addition, a subgroup analysis of all patients adhering to the label as assessed by the proxy based on diagnosis and contra-indications (as available) will be conducted.

6. Estimate the incidence rate of primary and secondary outcomes of interest between patients treated with NOCDURNA compared to a population of LUTS patients adjusted for confounding factors, by country where data available.

7. Estimate the incidence rate of cardiovascular and thromboembolic events of interest resulting in treatment withdrawal of NOCDURNA.

All secondary objectives will be evaluated in the overall population and among subgroups of interest (including elderly, aged ≥65 years).

Study design

Multi-country, cohort study using secondary data collected from research databases and administrative national healthcare registries in selected European countries: Denmark, Germany and Sweden. These countries have been selected following careful consideration of multiple factors: a feasibility assessment of the ability of candidate data sources to address the study objectives, recommendations by the Swedish Medical

Products Agency (MPA) and expected uptake of NOCDURNA in candidate countries of study.

Cohorts of patients with newly initiated treatment of NOCDURNA or with newly initiated treatment for LUTS will be identified from existing data sources in each country of study. If sample size permits, comparative analyses of incidence rate will be conducted for the primary and secondary outcomes of interest. The comparator group will be patients with LUTS. The incidence rate ratio (IRR) will be adjusted for by relevant confounding factors, such as age and gender (to be detailed in the statistical analysis plan (SAP)).

The study period will be between the launch of NOCDURNA and latest data availability in each country, considering that the final study report is planned for 2023. For each of the countries, the planned study periods are as follows: Denmark – 29 August 2016 to 31 December 2021; Germany – 1 January 2017 to 31 December 2021; and Sweden – 20 January 2017 to 31 December 2021. The difference in start of the study period across countries is dictated by the difference in NOCDURNA launch dates.

The index date for NOCDURNA patients is the dispensation date of the first dispensed prescription for NOCDURNA during the study period. For LUTS patients, the index is the date of first dispensed LUTS-defining drug in the study period.

Population

The cohort of NOCDURNA patients will consist of individuals meeting the following *inclusion criteria:*

- A first-ever dispensed prescription for NOCDURNA [desmopressin; Anatomical Therapeutic Chemical (ATC) code: H01BA02; brand name: NOCDURNA; dose: 25 or 50 microgram] recorded in the relevant country-specific data source between its launch date and the latest date of data availability in each country

- Aged 18 years and above on index date

- At least 12 months' registration in the relevant country-specific database(s) prior to the index date, to ensure a sufficiently long period of baseline data availability

Exclusion criteria:

The following exclusion criteria will be applied to the NOCDURNA cohort:

- Treatment with vasopressin or any of its analogues (defined as a dispensed prescription within 6 months before the index date; ATC codes H01BA), irrespective of formulation or dose/strength

- Multiple desmopressin drugs dispensed on the index date

The LUTS cohort will consist of individuals meeting the following *inclusion criteria:*

- At least one dispensed prescription for a medication used to treat urinary frequency and incontinence (ATC codes G04BD) or benign prostatic hypertrophy (ATC codes G04C) between the launch date of NOCDURNA and the latest date of data availability in each country.
- Aged 18 years and above at index date

Exclusion criteria:

The following *exclusion criterion* will be applied to the LUTS cohort:

- Treatment with vasopressin or any of its analogues (defined as a dispensed prescription within 6 months before the index date; ATC codes H01BA), irrespective of formulation or dose/strength

Subpopulations of interest:

Elderly patients (≥65 years of age at index) will be considered a subpopulation of special interest, for which separate analyses will be performed.

Furthermore, the following patient groups will be considered as subpopulations of special interest, as they are contraindications for NOCDURNA use. Numbers permitting, sub-analyses will be performed according to the NOCDURNA and the LUTS group overall and by the elderly.

- For the primary outcome:
  - History of hyponatraemia
  - Polydipsia
  - Concomitant use of loop diuretics
  - Concomitant use of glucocorticoids
  - Congestive heart failure (chronic)
  - Kidney disease (chronic kidney disease stage 3 and over)
  - Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Additionally, for the cardiovascular disease outcome: uncontrolled hypertension
- Additionally, for the thromboembolic event outcome: coagulation disorders

Variables

Exposure (based on dispensed prescriptions):

Exposure person-time will be defined for NOCDURNA patients from the date of first NOCDURNA prescription. For comparative analyses, equivalent person-time in the LUTS contextual cohort group will be defined from the index date.

Outcomes:

- Primary outcome:
  - Symptomatic hyponatraemia, as defined by a primary or secondary diagnosis of hyponatraemia (International Classification of Diseases, 10th Revision (ICD-10) code: E87.1) (In Germany: discharge diagnosis)

- Secondary outcomes
  - Hyponatraemia requiring hospital intensive care, defined as a primary or secondary diagnosis of hyponatraemia (ICD-10: E87.1) recorded in an intensive care unit
  - Clinically significant hyponatraemia, defined as a serum sodium concentration of <130 mmol/L. Hyponatraemia by level of severity (mild, moderate, severe) will be evaluated as part of this outcome.
  - All-cause mortality
  - Major adverse cardiovascular events (MACE), defined as a record of myocardial infarction and stroke. Fatal and non-fatal events will be considered separately.
  - Major venous thromboembolic events, defined as a record of a deep vein thrombosis, pulmonary embolism or portal vein thrombosis. Fatal and non-fatal events will be considered separately.
  - Acute exacerbation of congestive heart failure
  - MACE and VTE events resulting in treatment withdrawal of NOCDURNA

Covariates (assessed at the index date to the extent available in each data source):
- Demographics
- Treatment indication
- Comorbidities
- Co-medications
- Sodium concentration (Sweden/Denmark)

Data sources

Secondary data on exposure, outcomes and covariates will be collected from research databases and administrative national healthcare registries in Denmark, Germany and Sweden. In Denmark and Sweden, the national registries will be used. In Germany, the German Pharmacoepidemiological Research Database (GePaRD) based on insurance claims data will be used.

Study size

The primary objective is descriptive. All available patients with a NOCDURNA prescription in the study time period will be included in this study. Based on available sales data, the

number of NOCDURNA patients within the study time period is estimated to be at least 2650 for Germany (GePaRD), 2610 for Sweden, and 1830 for Denmark.

Data analysis

The incidence rate of the primary outcome reported since index date in the study observation period will be modelled using a Poisson regression model and expressed as number of cases per 1000 patients-years at risk (+95% confidence interval (CI)) for the NOCDURNA group and the LUTS contextual cohort, separately. The model will be adjusted for relevant strong risk factors for events of interest (gender, age (<65, 65-74, ≥75 years)), and stratum-specific incidence rates will be examined.

Separate Poisson regression models will be applied to (1) include only the first month after index date, and (2) include only subsequent months (month 2 after index and onwards), because Phase III pivotal clinical trials showed hyponatraemia incidence to be higher in the first month of treatment with NOCDURNA than after this time. For both the NOCDURNA and the LUTS group incidence rates will be estimated with 95% CI.

To investigate how the hazard of hyponatremia more precisely develops in time, hazard functions, based on Cox regression models for time to first event since index date will be plotted as a function of time.

Where possible, for the comparative analyses of primary and secondary outcomes of interest, the same analyses will be applied (Poisson regression) but now with the treatment group (NOCDURNA/LUTS) as a factor. To investigate if IRR depend on confounders, treatment by confounder interactions term will be investigated to see if and to what extent IRR depend on the respective confounding factor.

The same analyses conducted for the primary outcome of interest will also be applied for the secondary outcomes of interest.

Sensitivity analyses on the treatment episode definition will be performed to assess the robustness of the study findings.

The statistical analysis will be conducted using the SAS® software (version 9.3 or later) on Windows™ (SAS Institute, North Carolina, US) or using R program (version 3.5.0 or later).

Milestones

Study milestones are:

- Final study protocol in Q3, 2020
- Start of data collection in Q1, 2021
- Planned end of data collection in Q2, 2023
- Registration in the EU PAS Register in Q1, 2021
- Interim report(s) of study results in Q4, 2021; Q4, 2022

- Final report of study results in Q4, 2023

5 AMENDMENTS AND UPDATES

None

6 MILESTONES

Milestone	Planned date
Final study protocol	Q3, 2020
Start of data collection	Q1, 2021
Planned end of data collection	Q2, 2023
Registration in the EU PAS Register	Q1, 2021
Interim report(s) of study results	Q4, 2021; Q4, 2022
Final report of study results	Q4, 2023[1]

[1] Data updates have a lag period of up to 1.5 years. Data analysis and reporting will introduce a further lag of 6 months. Therefore, data included in the final report will likely be up to end of 2021.

7 RATIONALE AND BACKGROUND

Nocturia is defined as a complaint that an individual has to wake at night one or more times to void where each micturition is preceded and followed by sleep. Nocturia can be due to many factors, such as an underlying medical condition. However, some people experience nocturia due to idiopathic nocturnal polyuria, which means that although their total 24-hour production may remain normal, they produce an excessive amount of urine at night. Nocturia is a common cause of sleep disruption, and impaired sleep is associated with several serious short and long-term health effects. Studies have for example showed an association between sleep deprivation and obesity, diabetes, weakened immune system and some cancer types (1-5).

In 2016, Ferring Pharmaceuticals A/S, hereafter referred to as Ferring, finalised a decentralised procedure (DCP) in the European Union (EU) leading to the approval of NOCDURNA (desmopressin, gender-specific low doses of 25 µg for women and 50 µg for men) for the symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults. The active substance in NOCDURNA oral lyophilizate is desmopressin as desmopressin acetate (hereafter referred to as desmopressin), a synthetic analogue of the naturally occurring vasopressin, an antidiuretic hormone that promotes water re-absorption by the kidneys. The antidiuretic effect arises from its binding to the V_2-receptors in the renal collecting tubule, which results in increased water re-absorption in the collecting duct of the kidney and reduced volume of urine. Due to the low gender-specific doses of 25 µg for women and 50 µg for men, and the limited duration of action of NOCDURNA, the antidiuretic activity is limited to the night time sleep period.

Some safety concerns relating to NOCDURNA were defined during the EU DCP; risk of hyponatraemia (especially in elderly patients aged ≥65 years), a potential risk of thromboembolic events (though only expected at doses much higher than those recommended for NOCDURNA), and a potential risk of acute exacerbation of congestive heart failure in patients with chronic cardiac insufficiency. These safety concerns were based on data from clinical trials in haemophilia (OCTOSTIM, high-dose trials), post-marketing experience and general knowledge about pharmacodynamics and physiology of desmopressin. More specifically, the antidiuretic effect of desmopressin might lead to water retention and subsequently hyponatraemia through dilution of serum, if fluid intake is not limited. In phase 3 clinical trials with NOCDURNA, the incidence rate of clinically significant hyponatraemia (<130 mmol/L) was 2-3% in both genders (6, 7). A meta-analysis of data from three clinical trials of desmopressin in nocturia identified age ≥65 years, dose, low baseline serum sodium level and kidney function as significant risk factors for hyponatraemia in both sexes (8). This is similar to the risk factors associated with hyponatraemia in the general population. Furthermore, desmopressin at very high intravenous doses (equivalent to as much as 8,000 µg oral lyophilisate) increases the levels of some coagulation factors (factor VIII and von Willebrand factor) in the blood. Persistently increased endogenous factor VIII levels are a risk factor for venous thromboembolism (VTE). The evidence for elevated von Willebrand factor levels as a risk factor for VTE is less strong, but some studies have demonstrated an association (9). Finally, patients with heart failure already have abnormal water retention, hypo-osmolality,

and frequently hyponatraemia secondary to renal V_2-receptor activation. Due to the antidiuretic effect, desmopressin may lead to worsening of the fluid overload and to an increased risk of hyponatraemia in these patients. Consequently, heart failure is a contraindication to the use of NOCDURNA.

Against this background, the DCP member States have required that a post-authorisation safety study (PASS) is included in the NOCDURNA risk management plan to evaluate safety concerns and to collect long-term data in patients aged ≥65 years treated with NOCDURNA according to the approved summary of product characteristics (SmPC).

8 RESEARCH QUESTION AND OBJECTIVES

The overall objective of the present study is to increase the understanding of the long-term safety of NOCDURNA as used in routine clinical practice. This will be achieved by assessing the incidence risk and rate of hyponatraemia, cardiovascular (including acute exacerbation of congestive heart failure in patients with chronic cardiac insufficiency) and thromboembolic events among patients, in particular the elderly, treated with NOCDURNA. In addition, since it is desirable to put these observations into context and characterise a population with similar indications who do not receive desmopressin, a similar number of patients who are new users of standard care for other lower urinary tract symptoms (LUTS) will be evaluated in order to inform on the safety and utilisation of NOCDURNA.

Estimated incidence rates among NOCDURNA patients will be compared with incidence rates among a cohort of patients with newly initiated treatment for LUTS.

The **primary objective** is to

Estimate the incidence rate of symptomatic hyponatraemia (defined as a recorded diagnosis of hyponatraemia) among patients treated with NOCDURNA, and patients with LUTS separately, overall and by subgroups of interest (including elderly patients, aged ≥65 years).

The **secondary objectives** are to:

1. Describe the demographic and health characteristics of the population receiving NOCDURNA and patients with LUTS, including prevalence of risk factors for outcomes of interest.

2. Estimate the incidence rate of hyponatraemia requiring hospital intensive care among patients treated with NOCDURNA and patients with LUTS separately.

3. Estimate the incidence rate of clinically significant hyponatraemia (defined as a serum sodium concentration of <130 mmol/L) among patients treated with NOCDURNA and patients with LUTS separately.

4. Estimate the rate of all-cause mortality among patients treated with NOCDURNA and patients with LUTS separately.

5. Estimate the incidence rate of the following events of special interest among patients treated with NOCDURNA and patients with LUTS separately:
    a. Major cardiovascular events (composite endpoint)
    a. Major venous thromboembolic events (composite endpoint)

6. Estimate the incidence rate of acute exacerbation of congestive heart failure among patients who have chronic cardiac insufficiency treated with NOCDURNA, and patients with LUTS, separately.

7. In addition, a subgroup analysis of all patients adhering to the label as assessed by the proxy based on diagnosis and contra-indications (as available) will be conducted.
8.

9. Estimate the incidence rate of primary and secondary outcomes of interest between patients treated with NOCDURNA compared to a population of LUTS patients adjusted for confounding factors, by country where data available.

10. Estimate the incidence rate of cardiovascular and thromboembolic events of interest resulting in treatment withdrawal of NOCDURNA.

All secondary objectives will be evaluated in the overall population and among subgroups of interest (including elderly, aged ≥65 years).

9 RESEARCH METHODS

9.1 STUDY DESIGN

This is a multi-country, cohort study using secondary data collected from research databases and administrative national healthcare registries in selected European countries (Denmark, Germany and Sweden).

Cohorts of patients using NOCDURNA or treatment of LUTS (new user) will be identified from existing data sources in each country of study. These data sources hold information on dispensed prescriptions, patient demographics and diagnoses. The LUTS contextual cohort will be comprised of patients based newly starting treatments associated with polyuria, receiving relevant standard care. For secondary comparative analyses, the comparator group for NOCDURNA patients will be LUTS patients.

The study period will be from the date of launch of NOCDURNA until the date of latest data availability in each country, considering that the final study report is planned for 2023. Given the lag time of data updates and time allocated for analysis and reporting, last data included in the final report is likely to be up to end of 2021. Historical data, reflecting a minimum of 12 months before initiation of treatment with NOCDURNA (or initiation of treatment for LUTS), will be used to assess characteristics (e.g., demographics, indication, comorbidities and co-medication) at the index date.

In addition to the final study report, there will be annual interim reports (one per year) on study progress and any emerging safety data. Both country-specific and pooled results (meta-analysis) will be presented in the final report, where data are available.

9.2 SETTING

The study will be conducted among patients using NOCDURNA in the outpatient setting in three European countries: Denmark, Germany and Sweden. These countries have been selected following careful consideration of multiple factors: a feasibility assessment of the ability of candidate data sources to address the study objectives (please refer to section 9.5.2), recommendations by the Swedish Medical Products Agency (MPA), and expected uptake of NOCDURNA in the candidate countries. Sales data was used as an indicator of uptake of NOCDURNA to ensure a sufficiently large exposed population (Table 1). Based on the information contained in the data sources available in the candidate countries and the estimated extent of exposure to NOCDURNA based on available sales data in European countries, Denmark, Germany and Sweden were chosen as countries of study.

Table 1: NOCDURNA sales statistics (2018) and launch dates in candidate countries of study

Country	Share of NOCDURNA sales in 2018 (%)	NOCDURNA commercial launch date
Germany	40	January 2017
United Kingdom	22	November 2016
Belgium	9	March 2017
The Netherlands	7	November 2016
Sweden	7	January 2017
Denmark	5	August 2017

9.2.1 Duration of the study

The planned study period ranges from the date of launch of NOCDURNA (Table 1) to the date of latest data availability in each country. Thus, the planned study periods are as follows:

- Denmark: 29 August 2016 to 31 December 2021
- Germany: 1 January 2017 to 31 December 2021
- Sweden: 20 January 2017 to 31 December 2021

Historical data, reflecting a minimum of 12 months before index date will be used to assess baseline characteristics (e.g., demographics, comorbidities and co-medications). Thus, the total period for which data will be collected is from at least 12 months before the date of launch of NOCDURNA to the date of latest data availability in each country.

9.2.2 Cohort entry

Cohort entry is marked by the index date.

9.2.2.1 Index date - NOCDURNA cohort

The index date is defined by their first ever prescription of NOCDURNA in the study time period.

9.2.2.2 Index date - LUTS cohort

The index date is defined by their first ever prescription of medication used to treat urinary frequency and incontinence (Anatomic Therapeutic Chemical (ATC) codes G04BD) or benign prostatic hypertrophy (ATC codes G04C) in the study time period.

9.2.3 Cohort exit

9.2.3.1 Right censoring events – NOCDURNA cohort

Patients will be followed from the index date to the date of a censoring event: a dispensed prescription for a vasopressin agonist or desmopressin drug other than NOCDURNA, transfer out of the database, emigration, death or end of the study period, whichever occurs first and irrespective of treatment status (on/off drug). As appropriate, patient will also be followed from index date to the date of the diagnosis of the outcome of interest, or end of treatment of NOCDURNA (+7 days) as defined in section 9.3.1.

9.2.3.2 Right censoring events – LUTS cohort

Patients will be followed from the index date to the date of the censoring event: a dispensed prescription for a vasopressin agonist or desmopressin drug, transfer out of the database, emigration, death or end of the study period, whichever occurs first. As appropriate, patient will also be followed from index date to the date of the diagnosis of the outcome of interest, or the end of treatment of drugs defining the LUTS cohort, as defined in section 9.3.1.

9.2.4 Eligibility criteria

9.2.4.1 Inclusion criteria – NOCDURNA cohort

The cohort of NOCDURNA patients will consist of individuals meeting the following inclusion criteria:

- A first-ever dispensed prescription for NOCDURNA [desmopressin; Anatomical Therapeutic Chemical (ATC) code: H01BA02; brand name: NOCDURNA; dose: 25 or 50 microgram] recorded in the relevant country-specific data source between its launch date and the latest date of data availability in each country

Note: To identify NOCDURNA dispensations, first all desmopressin dispensations with the ATC code H01BA02 will be extracted, then the cohort for analysis will be selected using the brand name NOCDURNA and the dose of NOCDURNA (25 or 50 microgram).

- Aged 18 years and above on the index date
- At least 12 months' registration in the relevant country-specific database(s) prior to the index date, to ensure a sufficiently long period of baseline data availability

9.2.4.2 Exclusion criteria – NOCDURNA cohort

The following exclusion criteria will be applied to the NOCDURNA cohort:

- Treatment with vasopressin or any of its analogues (defined as a dispensed prescription within 6 months before the index date [index date -1 day]; ATC codes H01BA), irrespective of formulation or dose/strength

- Multiple desmopressin drugs dispensed on the index date

9.2.4.3 Inclusion criteria – LUTS cohort

Patients meeting the following criteria will be included in the LUTS cohort:

- A first-ever dispensed prescription for a medication used to treat urinary frequency and incontinence (ATC codes G04BD) or benign prostatic hypertrophy (ATC codes G04C) between the launch date of NOCDURNA and the latest date of data availability in each country

- Aged 18 years and above at index date

The ATC codes used to define the LUTS cohort are summarized in Annex 3 Definitions (Table A1).

9.2.4.4 Exclusion criteria – LUTS cohort

The following exclusion criterion will be applied to the LUTS cohort:

- Treatment with vasopressin or any of its analogues (defined as a dispensed prescription within 6 months before the index date [index date -1 day]; ATC codes H01BA), irrespective of formulation or dose/strength

9.2.5 Subpopulations of interest

Elderly patients (≥65 years of age at index) will be considered a subpopulation of special interest, for which separate analyses will be performed.

Furthermore, the following patient groups will be considered as subpopulations of special interest, as they are contraindications for NOCDURNA use. Numbers permitting, sub-analyses will be performed according to the NOCDURNA and the LUTS group overall and by the elderly.

For the primary outcome:
- History of hyponatraemia
- Polydipsia
- Concomitant use of loop diuretics
- Concomitant use of glucocorticoids
- Congestive heart failure (chronic)
- Kidney disease (chronic kidney disease stage 3 and over)
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

- Additionally, for the cardiovascular disease outcome: uncontrolled hypertension
- Additionally, for the thromboembolic event outcome: coagulation disorders

See Annex 3, Table A2 for diagnostic codes.

9.3 VARIABLES

9.3.1 Exposure

Person-time observed from index date to the date of outcome or censoring event will be determined for both the NOCDURNA group and the LUTS group.

Person-time exposed will start accumulating from the index date. For the NOCDURNA group this will be the date that the first-ever prescription for NOCDURNA was dispensed. Thus, this study will include patients who are new users of NOCDURNA. For the LUTS group, this will be the date of a first-ever prescription of a drug with the ATC code G04BD or G04C within the study time period. Thus, the LUTS groups will include patients who are new users of treatments for lower urinary tract symptoms.

Specific episode of exposure to NOCDURNA will be established using information on dispensed prescriptions for NOCDURNA. Information will include drug and substance name, ATC code, formulation, strength and dispensed amount of drug, as available in each data source.

On-treatment person-time will be constructed from single prescriptions or multiple sequential prescriptions for NOCDURNA and the drugs defining the LUTS cohort. The duration of individual prescriptions for NOCDURNA will be calculated based on the days supplied, as estimated from the number of oral lyophilisates dispensed and the recommended daily dosage, one oral lyophilisate per day. The estimated end date of a prescription will be the date it was dispensed plus the days supplied. Sequentially dispensed prescriptions for NOCDURNA will be bridged into continuous on-treatment episodes if each subsequent date the drug was dispensed was within the days supplied by the preceding prescription plus a period equivalent to the days supplied multiplied by 2 (*i.e.*, the permissible gap). In case of prescription overlaps, the number of overlapping days will be added to the estimated end date of the subsequent prescription. The first treatment period will end when there is no subsequent prescription dispensed within the days supplied from the preceding prescription plus the defined permissible gap. Prescriptions of LUTS-defining drugs (ATC code G04BD or G04C) will be treated analogous to NOCDURNA in terms of permissible gap. Treatment restarts following treatment holiday will not be evaluated in this study.

9.3.2 Outcomes

The primary and secondary outcomes presented below are also summarized in Table 2.

9.3.2.1 Primary outcome

The primary outcome is symptomatic hyponatraemia, as defined by a primary or secondary diagnosis of hyponatraemia (ICD-10 code: E87.1) recorded in Sweden and Denmark, and by a discharge diagnosis in the German Pharmacoepidemiological Research Database (GePaRD). Thus, diagnoses from within hospital inpatient and specialist outpatient care will be considered in the Swedish and Danish data sources (see section 9.4 for information on data sources). Primary and secondary diagnoses of hyponatraemia will be considered equally important in the Swedish and Danish data sources. In the German GePaRD, all outpatient diagnoses will be considered.

An incident event is defined as the first record of symptomatic hyponatraemia during each patient's follow-up. The incidence rate of the primary outcome will be modelled using Poisson regression. If, however unlikely, recurrent events of symptomatic hyponatremia have been observed, a Cox model for recurrent events may be applied.

9.3.2.2 Secondary outcomes

The secondary outcomes for this study are the following events:

1. Hyponatraemia requiring hospital intensive care, defined as a primary or secondary diagnosis of hyponatraemia (ICD-10: E87.1) recorded in an intensive care unit.

   This outcome will only be evaluated in Sweden using data collected from the Swedish Intensive Care Registry (SIR; see section 9.4.3.4), as information to distinguish between hospital inpatient care in general and intensive care in particular is not available in the Danish national registries or the German GePaRD (see sections 9.4.1 and 9.4.2, respectively).

   Only incident events (first hyponatraemia record from within hospital intensive care during follow-up) will be considered.

2. Clinically significant hyponatraemia, defined as a serum sodium concentration of <130 mmol/L (10).

   In addition, hyponatraemia by level of severity will be evaluated, where *mild* hyponatraemia is defined as a serum sodium concentration of 130-<135 mmol/L, *moderate* as a serum sodium concentration of >125-<130 mmol/L, and *severe* as a serum sodium concentration of ≤125 mmol/L.

   Clinically significant hyponatraemia, including level of severity, will only be assessed in Denmark using data collected from the Danish National Laboratory Database Research Table. The evaluation of this outcome will be restricted to patients residing in the four Danish regions covered by the database (see section 9.4.1.4).

   Incident and recurrent events will be considered and analysed separately.

3. All-cause mortality, defined as death from any cause.

   This outcome can be evaluated in all data sources: Denmark and Sweden using the national cause of death registries (see sections 9.4.1.5 and 9.4.3.5), and in Germany using the date of death.

4. Major adverse cardiovascular events (MACE (11)), defined as a record of myocardial infarction and stroke, (see Annex 3, Table A3, for a list of diagnosis codes used to define these conditions) recorded in each relevant country data source. In Sweden and Denmark, fatal events of myocardial infarction and stroke are also considered as MACE (as cause of death is available). MACE is a composite endpoint.

   In addition to overall MACE events, MACE requiring hospital intensive care defined as defined as a primary or secondary diagnosis of MACE recorded in a hospital intensive care unit will be reported in Sweden.

5. Major venous thromboembolic (VTE) events, defined as a record of a deep vein thrombosis, pulmonary embolism or portal vein thrombosis (see Annex 3, Table A3, for a list of diagnosis codes used to define these conditions) recorded in each relevant country data source. In Sweden and Denmark, fatal events of VTE are also considered (as cause of death is available). VTE is a composite endpoint.

   In addition to overall VTE events, VTE events requiring hospital intensive care defined as defined as a primary or secondary diagnosis of VTE events recorded in a hospital intensive care unit will be reported in Sweden.

   Fatal and non-fatal MACE and VTE events will be assessed separately. Fatal events will only be assessed in Denmark and Sweden using the national registries. Information on cause of death is not available in the German GePaRD. For fatal events, death from a MACE or VTE event recorded as the underlying or contributory cause will be considered. For non-fatal MACE and VTE events, primary and secondary diagnoses will be considered equally important (in Germany: discharge diagnoses). Incident events of MACE and VTE in the study time period will be analysed.

6. Acute exacerbation of congestive heart failure

   Given that cardiac insufficiency is a contraindication for the use of NOCDURNA, the incidence of acute exacerbation of congestive heart failure among patients who

have chronic cardiac insufficiency is considered an exploratory outcome in this study.

This outcome will only be analysed among patients with prevalent chronic heart failure. Prevalent chronic heart failure will be defined as ever having had a primary or secondary diagnosis of heart failure (ICD-10: I50; in German GePaRD: outpatient or inpatient diagnosis) before the index date, but no recorded primary diagnosis of heart failure from hospital inpatient care or the acute and emergency ward in the 6 months prior to the index date (German GePaRD: discharge diagnoses). Among these patients, acute exacerbation of heart failure will be defined as a primary diagnosis of acute or acute-on chronic heart failure from hospital inpatient care or the acute and emergency ward, or death from heart failure as the underlying or contributory cause. Non-fatal events of acute exacerbation of heart failure will be evaluated in all three countries, while fatal events will only be evaluated in Denmark and Sweden.

In addition, a subgroup analysis of all patients adhering to the label as assessed by the proxy based on diagnosis and contra-indications (as available) will be conducted.

7. MACE and VTE events resulting in treatment withdrawal of NOCDURNA

Serious events resulting in treatment withdrawal of NOCDURNA will be evaluated in the NOCDURNA exposed group only. Treatment cessation of NOCDURNA, defined by a time after prescription longer than the permissible gap (see section 9.3.1), will be defined as the end of an on-treatment period. Serious events will be evaluated in 14 days prior to the treatment cessation date.

Serious MACE and VTE events will be defined as a primary or secondary diagnosis of MACE or VTE recorded in a hospital intensive care unit. This can be only evaluated in Sweden.

Table 2: Definitions of primary and secondary outcome variables

Variable	Definition	Countries in which outcome assessed
Primary outcome		
Symptomatic hyponatraemia	Primary or secondary diagnosis of hyponatraemia (E87.1)	• Denmark • Germany (hospital discharge diagnosis) • Sweden
Secondary outcomes		

Variable	Definition	Countries in which outcome assessed
Hyponatraemia requiring hospital intensive care	Primary or secondary diagnosis of hyponatraemia (E87.1) from hospital intensive care	• Sweden
Clinically significant hyponatraemia including hyponatraemia by severity	Serum sodium concentration <130 mmol/L Mild hyponatraemia: serum sodium concentration 130-<135 mmol/L Moderate hyponatraemia: serum sodium concentration >125-<130 mmol/L Severe hyponatraemia: serum sodium concentration ≤125 mmol/L	• Denmark
All-cause mortality	Death from any cause	• Denmark • Sweden • Germany
Major cardiovascular events	Primary or secondary diagnosis of cardiovascular death (underlying or contributory cause), myocardial infarction or stroke	• Denmark • Germany (non-fatal events only; discharge diagnosis) • Sweden
Major venous thromboembolic events	Primary or secondary diagnosis of deep vein thrombosis, pulmonary embolism, portal vein thrombosis, *or* death from either of these conditions as the underlying or contributory cause	• Denmark • Germany (non-fatal events only; discharge diagnosis) • Sweden
Acute exacerbation of congestive heart failure	Primary diagnosis of acute or acute-on-chronic heart failure from hospital inpatient care or the acute and emergency ward, or death from heart failure as the underlying or contributory cause	• Denmark • Germany (non-fatal events only; discharge diagnosis) • Sweden
Serious adverse events	Primary or secondary diagnosis of MACE or VTE leading to admission to a hospital intensive care unit	• Sweden

9.3.3 Covariates

To describe the study population, information on following variables will be collected to the extent available in each data source for a period of at least 12 months before the index date:

- Demographics: age, gender, place of residence (country), migration or transfer out of the database

- Treatment indication (diagnosis preceding NOCDURNA prescription in the exposed group; diagnosis preceding LUTS-defining prescription in the LUTS patient group)

- Sodium concentration (Sweden/Denmark)

- Comorbidities

- Co-medications

These factors may be considered in the analysis as potential confounding factors or effect modifiers. The comorbidities and co-medications are to be measured by disease and drug codes are specified and defined by classification system codes in Annex 3 Definitions (Table A4). Refer to section 9.4 for description of data sources that will be used to collect information on covariates.

9.4 DATA SOURCES

All patient information on exposure, outcomes and covariates will be obtained from existing data sources.

To meet the study objectives, the following data sources will be considered.

9.4.1 Denmark

All individuals living in Denmark (for at least 3 months) has a unique personal identity number, the so-called CPR (Central Person Registry) number, which also carries information on the date of birth and gender. All the registers listed below have information of the CPR number, enabling linkage of the different registers.

9.4.1.1 The Danish Civil Registration System (DCRS)

The Danish Civil Registration System (DCRS), managed by the Central Office of Civil Registration, holds basic demographic information on all individuals living in Denmark (12). For each individual, the information includes personal identity number (PIN), date of birth, vital status, place of birth, place of residence, and date of death or emigration. Access to data for scientific purposes is applied for from the Danish Health Data Authority. The DCRS will be used to collect information on vital status and emigration for the Danish patients.

9.4.1.2 Danish Registry of Medicinal Products Statistics (DRMPS)

This national registry, managed by the Danish Health Data Authority, covers virtually 100% of the Danish population (5.7 million in 2017). The registry has data available since 1995 on all prescribed medication dispensed from community pharmacies (13). The registry contains information on date of purchase and product name, ATC code, defined daily dose (DDD) and number of packages purchased of the drug. The prescribed dose and/or the indication, however, are only available as an optional free-text instruction to the patient. Data are updated on a monthly basis with a lag time of 2-3 months for data availability.

Access to the registry data for scientific research is granted by the Danish Health Data Authority. The applicant must be a Danish public research organisation. All data analyses using the registry (and linked) data must be conducted at the closed research servers of the Danish Health Data Authority or Statistics Denmark. The DRMPS will be used to identify the cohort of NOCDURNA patients and assess other medication use among the NOCDURNA patients and the LUTS cohort.

9.4.1.3 Danish National Patient Registry (DNPR)

This national registry, also managed by the Danish Health Data Authority, covers virtually 100% of the Danish population (5.7 million in 2017) admitted to Danish somatic hospitals, emergency rooms, and specialty outpatient clinics (secondary care) (14). The DNPR holds data on admissions to hospitals since 1977 and on emergency rooms and outpatient clinics since 1995. Data from primary care and psychiatric care are not included. For each hospital contact, the registry includes information on date of admission and discharge, diagnoses made (coded in ICD codes), setting of care, and surgical and non-surgical procedures. Data for the previous year is usually available in March. Access to the registry data for scientific research is applied from the Danish Health Data Authority. The DNPR will be used to ascertain outcome events and to assess comorbidities.

9.4.1.4 Danish National Laboratory Database Research Table

This database holds data on laboratory tests conducted at major clinical biochemistry and clinical immunology laboratories in Denmark (15). Private hospitals are not covered by the database. It is held by the Danish Health Data Authority. With respect to clinical biochemistry, the database covers four Danish regions (Northern Jutland, Southern Denmark, Capital and Zealand), encompassing 4.4 million residents or nearly 80% of the total population (2017). Start of data availability varies by region, with the earliest clinical biochemistry data becoming available in the fourth quarter of 2013 and the latest in the third quarter of 2015. Only laboratory test results coded to the Nomenclature for Property and Unit (NPU) or DNK systems are included in the database. The test measurement unit and the date when the sample taken are recorded. Data is updated monthly and can be accessed for scientific research purposes by application to the Danish Health Data Authority. This database will be used to ascertain outcome events.

9.4.1.5 Danish Registry of Causes of Death (DRCD)

This registry, managed by the Danish Health Data Authority, holds data on deaths in Denmark since 1968, with a reporting rate of close to 100% (16). Included in the information is time and cause of death and post-mortem examinations. Data is updated annually and is available with a lag of approximately 12 months. Access to the registry data for scientific research is possible via application to the Danish Health Data Authority. The DRCD will be used to ascertain outcome events.

9.4.2 Germany

The German Pharmacoepidemiological Research Database (GePaRD) consists of claims information from providers of statutory health insurance (SHI) in Germany (17). GePaRD currently holds data on more than 25 million individuals who have been insured with one of the participating providers since 2004 or later. Per data year, the database includes information on approximately 17% of the general population from all geographical regions of the country. The database was established in 2004 and is managed by the Leibniz Institute for Prevention Research and Epidemiology (BIPS GmbH). The database comprises information on all reimbursable drug dispensations and all reimbursable outpatient (i.e., from general practitioners and specialists) and inpatient diagnoses and services as well as demographics. The ICD-10-GM and ATC coding systems are used for diagnosis and dispensation data, respectively. Additional pharmaceutical information can be obtained through linkage of the central pharmaceutical number in GePaRD to the respective ATC code and additional information (e.g. brand, manufacturer, number of units and strength of unit). The GePaRD database is regularly used for pharmacoepidemiological research. Information can be accessed upon collaboration and study specific approval with BIPS for projects with public health interest and scientific relevance.

9.4.3 Sweden

The study will include data from several nationwide registries. Patient-level data will be linked across the registries using the unique PIN assigned to each Swedish citizen or person resident in Sweden. The Swedish national registries contain records for the entire Swedish population making it possible to create large and powerful cohorts (18). The patient record linkage will be carried out by the National Board of Health and Welfare (NBHW) and Statistics Sweden, which are the holders of the Swedish national registries to be used in this study. Through the patient record linkage, a tailored study database will be created. The linked datasets will be pseudonymised before the sponsor representative can access them.

9.4.3.1 Swedish Total Population Registry (STPR)

The Total Population Registry in Sweden is held by Statistics Sweden and includes all individuals living in the country with individual-level information on the date of birth (PIN), gender, country of birth, place of residence, dates of any emigration and immigration events, and date of death (19). The STPR will be used to collect migration data for the Swedish patients.

9.4.3.2 Swedish Prescribed Drug Registry (SPDR)

All medications that have been prescribed and later dispensed in community pharmacies to individual patients are recorded in the SPDR (20, 21). The register covers all pharmacy transactions starting in July 2005. Gender, age and residency of the patients are recorded in the SPDR, as is drug-specific information on prescription and dispensing dates, ATC

code, active substance, product name, strength, pack size, dispensed quantity and the specialty of the prescribing physician, etc. The SPDR is held by the NBHW and is updated monthly; data can be accessed with only a few weeks' delay. The SPDR will be used to identify the cohort of NOCDURNA patients and assess other medication use among the NOCDURNA patients and the LUTS cohort.

9.4.3.3 Swedish National Patient Registry (SNPR)

Data from hospital inpatient and specialist outpatient care (secondary care) in Sweden can be collected from the National Patient Registry (SNPR), which is also held by the NBHW. The SNPR started in 1964. There has been national coverage of all completed inpatient stays since 1987. Since 2001, the register also holds nationwide specialist outpatient data. Key information recorded in the register relates to the patient (PIN, gender, age, place of residence), geographical data (county council, hospital/clinic, department), the visit or stay as such (admission and discharge dates, length of stay, etc) and medical data [primary and secondary diagnoses (coded in ICD codes), procedures, etc] (22). The SNPR is updated annually, with data from the previous statistical year becoming available with a delay of at least 7 months. This registry will be used to ascertain outcome events and assess comorbidities.

9.4.3.4 Swedish Intensive Care Registry (SIR)

SIR is a quality registry that was established in 2001 with the purpose of improving intensive care in Sweden (23). SIR is held by the county council of Värmland and managed by a steering committee. Data completeness has improved gradually over the years. In 2017, 80 of 84 (95%) intensive care units (ICUs) in Sweden reported data to SIR. Key information held in SIR includes the PIN, gender, age, type of ICU, diagnoses (coded to ICD-10) recorded while admitted to ICU and vital status at discharge from ICU. Data is updated weekly, with full-year data becoming available with a lag of approximately two months.

9.4.3.5 Swedish Cause of Death Registry (SCDR)

The Swedish Cause of Death Registry (SCDR) started in 1961 and is held by the NBHW. It includes information of causes of death for all residents in Sweden, whether or not the deceased was a Swedish citizen and the death occurred in Sweden or abroad. The quality of the cause of death statistics varies, due to the examinations made to define the underlying cause of death, changes in the classification system and processing methods. Key variables included in the registry are the PIN, gender, date of death, underlying cause of death, and contributing cause(s) of death (24). Data on date of death is available with little delay (approximately real-time), while data on cause of death is updated annually with a delay of approximately 10 months from the previous statistical year. The SCDR will be used to ascertain outcome and censoring events.

9.5 STUDY SIZE

9.5.1 Determination of sample size

The study will use data from countries where the uptake of NOCDURNA is expected to provide a sufficiently large population of exposed patients. Therefore, the sampling frame has been constructed using the distribution of sales data in the EU (see Table 1).

9.5.2 Feasibility assessment

A feasibility assessment was conducted to investigate the appropriateness of candidate countries and data sources for completion of this study. A full quantitative assessment based on actual data extractions was conducted in four countries: Belgium (Longitudinal Patient Database (LPD)), Germany (Disease Analyzer (DA)), Sweden (national registries) and the UK (The Health Improvement Network, THIN). A high-level qualitative assessment based on desk research was carried out for the Netherlands (PHARMO database). Each data source was evaluated on the following main aspects:

- The number of eligible patients, *i.e.*, patients treated with NOCDURNA who have 12 months of baseline data available prior to the first recorded prescription during the study period.
- The availability and validity of variables of interest.

Detailed results from the feasibility assessment can be found in the Summary of NOCDURNA extended feasibility study. An overview of the findings is presented below (Table 3). The general rating of the countries showed that the top 3 countries, excluding the Netherlands (where the detailed assessment has not been carried out), were Sweden, Germany and the UK.

The final choice of countries and appropriate data sources was, however, not made until scientific advice provided by the Swedish MPA had been considered. It was decided not to use the UK data source for this study, as the number of patients with NOCDURNA prescriptions and relevant laboratory values was too low. It was recommended based on sales data and previous knowledge of available variables in Danish registry data, that UK THIN would be replaced with Danish national registries as a data source.

It was also noted, that a large proportion of NOCDURNA sales is in Germany, but only a small number of patients was captured in the German DA data source. This could potentially be due to the data being collected form primary care, whereas most NOCDURNA prescriptions may occur in a specialist setting. Therefore, GePaRD was recommended as an alternative data source for Germany.

The sponsor and sponsor representative agreed that the Danish national registries and German claims database GePaRD would replace the German DA and UK THIN databases. The final countries of study are thus Denmark, Germany and Sweden.

Table 3: General data availability by country evaluated in the feasibility assessment

Data aspect[1]	**Belgium *LPD***	**Germany *DA***	**Sweden *NHRs***	**Netherlands *PHARMO***	**UK *THIN***
Number of eligible patients treated with NOCDURNA[2]	9	174	704	N/A	46
Issued prescriptions (primary care)	Yes	Yes	Yes[3]	Yes	Yes
Issued prescriptions (secondary care)	No	Yes	Yes[3]	No	No
Filled prescriptions (primary care)	No	No	Yes	Yes	No
Filled prescriptions (secondary care)	No	No	Yes	Yes	No
Prescription duration	Yes	Yes	Yes	Yes	Partial
Daily dose	Yes	Yes	Yes	Yes	Yes
Diagnoses primary care	Yes	Yes	No	Yes	Yes
Diagnoses secondary care	No	Yes	Yes	Partial	Yes
Possibility to link primary and secondary care data	No	No	Yes	Yes	No
Possibility to distinguish between primary and secondary diagnosis	Yes	Yes	Yes	Yes	Yes
Possibility to identify treatment in the intensive care unit	No	No	Yes	No	No
Lab test date	Yes	Partial	No[4]	Yes	Yes
Lab test results	Yes	Partial	No[4]	Yes	Yes
Date of death	No	No	Yes	Yes	Yes
Cause of death	No	No	Yes	No	No
Overall rating (0-15)[5]	**7**	**8**	**12**	**11.5**	**8.5**

DA, Disease Analyzer; LPD, Longitudinal Patient Database; N/A, not applicable; NHRs, National health registers; THIN, The Health Improvement Network.
[1] Reported as ”yes” if available, ”no” if not and “partial” if available partially for all data aspects except number of eligible patients.
[2] For each country, assessed from launch of NOCDURNA to latest date of data availability.
[3] Only available if prescription was filled.
[4] Only available if electronic medical records are extracted, not available in the national registers.
[5] Rating indicates the total number of data aspects available; 1 was given for ”yes”, 0.5 for ”partial” and 0 for ”no”.

9.5.3 Sample size for primary outcome analysis

All available patients with a NOCDURNA prescription in the study time period will be included in this study. The primary objective is descriptive.

In addition to the feasibility study detailed above, NOCDURNA sales data was reviewed to estimate the available number of patients. Table 4 shows the patient estimate based on the share of NOCDURNA sales in 2018, the number of oral lyophilisates, 50% adherence, and coverage of the database per country of this study. GePaRD coverage is approximately 18% of the German population.

Table 4. Patient estimate for 2018 per country of interest

Country	Share of NOCDURNA sales in 2018 (%)	Number of oral lyophilisates	Patient estimate assuming 50% adherence	Patient estimate from the Database
Germany	40	661.950	3.678	662
Sweden	7	117.250	651	651
Denmark	5	82.260	457	457

The patient estimate for Sweden is thus in line with the results from the feasibility study. That the coverage and availability of data from Denmark is comparable to Sweden, as both data sources rely on national registers. Taking into account the switch from the DA to GePaRD database in Germany, the order of magnitude of available patients is also in line with feasibility results from Germany.

Extrapolating the patient estimated from Table 4 to a time period 2018-2021 (end of the study time period), and assuming conservatively that sales remain constant during the time period, the number of NOCDURNA patients in this study will likely be at least:

- Germany (GePaRD): 2650
- Sweden: 2610
- Denmark: 1830

9.6 DATA MANAGEMENT

The data used in this study will be collected from national or regional healthcare providers/authorities or other database holders.

In Denmark, the administrative national registers are held by the Danish Health Data Authority. Access to data will be obtained by the principal investigator through either of the safe research server environments provided by, respectively, the Danish Health Data

Authority and Statistics Denmark. Data from the different registers will be extracted, linked, and anonymised by the research service unit at the authority providing the data access.

Data from the German GePaRD cannot be directly accessed by third parties. The German part of the study will therefore be conducted through collaboration with BIPS (Leibniz Institute for Prevention Research and Epidemiology – BIPS), who will seek approval for the study from the statutory health insurance providers and their governing authorities. The data collected will be analysed by BIPS as described in this study protocol and the subsequently developed statistical analysis plan (SAP). Only aggregated-level data will be shared with third parties.

In Sweden, approval for the study will be sought from the Swedish Ethical Review Authority. Once approval has been granted, access to data is obtained by the principal investigator through written request to the respective data holders. Statistics Sweden and the NBHW are the data holders of the national administrative registries. Access to data from SIR will be sought by application directly to this quality registry. SIR data will be sent by the registry holder to the NBHW for linkage. The NBHW will create a source population in accordance with the protocol and establish linked data sets including all registry data obtained for the Swedish part of the study. Patient-level data collected from national or regional healthcare providers/authorities will be pseudonymised before accessed by the sponsor representative. Thus, the integrity of individual patients is protected.

Data management and statistical analyses performed within sponsor representative facilities will be conducted using appropriate statistical software.

9.7 DATA ANALYSIS

The statistical analyses described below may be revised and adjusted and will be further detailed in the SAP. The final SAP version will include (empty) table shells to be populated for the study report(s).

9.7.1 General considerations

Given between-country differences in the type of data used, governance regulations and patient privacy rules, and expected variations in the background risk of diseases, the countries will be analysed separately and combined in a meta-analysis (where the estimates for each country and cohort will be pooled, as applicable). The meta-analysis will be performed for the final report only. Any heterogeneity in results across the countries of study will be handled by using a random-effects model.

The distribution of continuous variables (age) will be examined graphically using boxplots, symmetry plots, normal quantile plots and normal probability plots. Exploratory analyses to provide insight into general patterns will be conducted using number and percent within each category with 95% confidence interval (CI) for categorical variables except cohort characteristics, and mean (standard deviation, SD), median (interquartile range, IQR), and other relevant summary statistics for continuous variables. Where appropriate, a log transformation of continuous variables (age) will be applied to handle skewness (back-

transformed prior to reporting) or a non-parametric approach will be adopted if there is no appropriate transformation. Quantitative variables may be categorised into quartiles as required.

Missing data for covariates will be described. Since missing values are expected to be few and distributed at random, in general, no replacement or imputation will be performed. Missing values will not be considered in the denominators for proportions.

The statistical analysis will be conducted using the SAS® software (version 9.3 or later) on Windows™ (SAS Institute, North Carolina, US) or using R statistical program (version 3.5.0 or later).

9.7.2 Primary analysis

All descriptive analyses outlined below will performed in the NOCDURNA cohort, the LUTS group, and stratified by subgroups of interest.

9.7.2.1 Primary objective: Incidence of symptomatic hyponatraemia

The incidence rate of the primary outcome reported since index date in the study observation period will be modelled using a Poisson regression model and expressed as number of cases per 1000 patients-years at risk (+95% CI) for the NOCDURNA group and the LUTS contextual cohort, separately. Person-period at risk is defined according to person-time observed from the index date to the first right censoring event. The numerator will comprise of reports of incident symptomatic hyponatraemia during the observation period. The model will be adjusted for relevant strong risk factors (gender, age (<65, 65-74, ≥75 years). Stratum-specific incidence rates will also be examined. These will be detailed in the SAP.

As in Phase III pivotal clinical trials incidence of hyponatremia is observed to be higher in the first month of treatment with NOCDURNA than in the subsequent months, two separate Poisson regression models will be applied: (1) including only the first month after the index date, and (2) including only subsequent months after the index date (month 2 and onwards). Recurrent events of hyponatremia are not expected in NOCDURNA patients, as treatment should be discontinued after symptomatic hyponatremia has been diagnosed. For both the NOCDURNA and the LUTS group incidence rates (number of events/ 1000 person-years) will be estimated with 95% CIs.

To investigate how the hazard of hyponatremia more precisely develops in time, hazard functions, based on Cox regression models for time to first event since index date (using the same regressors as in the Poisson model) will be plotted as a function of time.

If, however unlikely, recurrent events have been observed, a Cox model for recurrent events may be applied which will be detailed in the SAP.

9.7.2.2 Secondary objective 1: Demographic and health characteristics

Demographic characteristics will be presented for both the NOCDURNA and LUTS cohorts based on the index date. Other co-existing risk factors for primary and secondary outcomes of interest will also be summarised. Characteristics will be described overall by cohort and stratified by sub-populations of interest.

9.7.2.3 Secondary objective 2: Incidence of hyponatraemia requiring hospital intensive care

The analysis of hyponatraemia requiring hospital intensive care will be performed analogously to the analysis of incident events of symptomatic hyponatraemia (see 9.7.2.1).

9.7.2.4 Secondary objective 3: Incidence of clinically significant hyponatraemia

Analyses of incident and recurrent events of clinically significant hyponatraemia will be performed analogously to symptomatic hyponatraemia (see 9.7.2.1). Analyses will be performed among patients residing in the regions covered by the Danish National Laboratory Database Research Table (see section 9.4.1.4).

The potential lack of serum sodium measurements, differences in the likelihood of being tested and intensity of testing will be addressed by describing the distribution of risk factors and background characteristics (e.g., relevant demographic and other risk factors such as comorbidities and co-medication) for tested and non-tested patients.

9.7.2.5 Secondary objective 4: All-cause mortality

The analysis of all-cause mortality will be performed analogously to that of incident events of symptomatic hyponatraemia, from the index date (see 9.7.2.1).

9.7.2.6 Secondary objective 5a: Incidence of major cardiovascular events

The analysis of incident MACE will be performed analogously to that of incident events of symptomatic hyponatraemia (see 9.7.2.1), from index date. Fatal and non-fatal MACE and VTE events will be assessed separately.

In addition, time to events requiring hospital intensive care and cardiovascular death, respectively, will be described for patients with an incident diagnosis of MACE in the study time period. Events requiring hospital intensive care will be defined as a primary or secondary diagnosis of MACE recorded in a hospital intensive care unit (reported in Sweden only). Cardiovascular death is defined as a relevant diagnosis recorded as the underlying or contributing cause of death (reported for Sweden and Denmark).

9.7.2.7 Secondary objective 5b: Incidence of major venous thromboembolic events

The analysis of incident VTE events will be performed analogously to that of incident events of symptomatic hyponatraemia (see 9.7.2.1), from index date.

Similar to MACE, time to events requiring hospital intensive care and death from a VTE event, respectively, will be described for patients with an incident diagnosis of VTE in the study time period.

9.7.2.8 Secondary objective 6: Incidence of acute exacerbation of congestive heart failure

The analysis of this outcome will be performed analogously to that of incident events of symptomatic hyponatraemia (see 9.7.2.1).

9.7.2.9 Secondary objective 7: Comparative analyses

Where possible, for the comparative analyses of primary and secondary outcomes of interest, the same analyses (Poisson regression) as in Section 9.7.2.1 will be applied but now with treatment group (NOCDURNA/LUTS) as an additional factor. To investigate if the incidence rate ratio (IRR) for the Poisson regression of NOCDURNA to LUTS depend on confounders, treatment by confounder interaction terms will be investigated to see if and to what extent (quantitative or qualitative) the IRR depend on the respective confounding factor. These multiple regression methods will be detailed in the SAP.

9.7.2.10 Secondary objective 8: Cardiovascular and thromboembolic events of interest resulting in treatment withdrawal

The analysis of this outcome will be performed analogous to that of incident events of symptomatic hyponatraemia (see 9.7.2.1) for NOCDURNA only. MACE and VTE events considered to be associated with treatment cessation will be those events for which the event date occurs within 14 days prior to the treatment cessation date (see section 9.3.1). Serious MACE and VTE events will be defined as a primary or secondary diagnosis of MACE or VTE recorded in a hospital intensive care unit. This can be only evaluated in Sweden.

9.7.2.11 Secondary objective 9: Incidence rate in patients stratified according to the label by proxy

The analysis of this outcome will be performed analogous to that of incident events of symptomatic hyponatraemia (see 9.7.2.1) for NOCDURNA only. The subgroup of patients adhering to the label will be defined by a proxy based on diagnosis and contra-indications as available in the respective registries. This will be detailed in the statistical analysis plan

In this analysis the outcomes specified as the primary objective and secondary objectives 1-6 will be repeated for the NOCDURNA only patients. The subgroup of patients adhering to the label will be defined by a proxy based on diagnosis and contra-indications as available in the respective registries based on the information in the SmPC. Two population will be created for all NOCDURNA patients, one with contra-indication for treatment and another as the remaining NOCDURNA patients without contra-indication. The contra-indication for treatment must be present before the first recorded dispensation of NOCDURNA. This approach will be detailed in the statistical analysis plan

9.7.3 Sensitivity analyses

Sensitivity analyses will be performed to assess the robustness of the study findings:

- The assumptions underlying the construction of NOCDURNA treatment episodes will be tested. The length of the permissible gap will be varied (shortened or lengthened). For overlaps of two subsequent prescriptions, beginning of the second prescription will be shifted to the end of the first. The estimation of prescription duration will also be examined. Instead of estimating prescription duration based on the recommended daily dose of NOCDURNA (1 oral lyophilisate), the dose actually prescribed to the individual patient will be considered (Sweden, Denmark). This analysis will be subject to availability of data on individual dosage instructions in the database/registry.

9.7.4 Meta-analyses

Assuming country-specific analyses have been completed, results for the analysis of primary and secondary outcomes that can be defined in all three countries can also be combined using a meta-analysis approach in order to achieve a more precise estimate of the observed measure of incidence rate and identify any potential country-specific patterns in the data. Incidence rates of the two different groups will be combined across the three databases. Because the current analysis will pool incidence proportions of sparse data, a logistic regression model with random intercept will be used to calculate the pooled the mean log odds, which will be back transformed to the probability scale to yield the median incidence proportion and 95% CI. A likelihood ratio test will be used to evaluate between-database heterogeneity. Database-specific incidence rates will be meta-analysed with a Poisson regression model with random intercept (25). The logarithm of the sum of patient-time at risk will be used as an offset variable to yield incidence rates per 1000 patient-years. Pooled incidence rates will be back-transformed from the logarithm scale to per 1000-patient-years unit.

9.8 QUALITY CONTROL

9.8.1 Data collection, validation and data quality control at level of sponsor representative

Data collected from claims databases and administrative (national) healthcare registries and databases in Denmark, Germany and Sweden will be used to retrieve data on the selected patient population. These are all data sources that are being used widely for research.

GePaRD is based on deterministically linked claims data. The linkage of out-patient, hospital and dispensation data is performed at each SHI provider (based on insurance member identifiers. The SHIs deliver the data to a third-party trust centre where the data is pseudonymised and delivered to BIPS according to the data protection concept. Comprehensive plausibility checks are performed before pseudonymisation, as well as before inclusion of new data into GePaRD.

In Sweden and Denmark, national registers are governed by the respective national boards of health and the national statistics agencies. In both countries, reporting of information to the health data registers is compulsory for all healthcare providers. Rigorous validation work is constantly ongoing from the health authorities to ensure that data are complete, comprehensive and with the highest quality possible. The data sources used in this project have been used extensively for research. Data quality will be further checked and assessed in the data management process. Moreover, the investigator will stay in close dialogue with the register holders to assure accuracy in the data retrieved.

9.8.2 Quality control of results

The study will be conducted according to best-practice guidelines applicable to studies, including but not limited to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP).

BIPS adheres to high standards throughout the research process based on robust methodologies, transparency and scientific independence. BIPS conducts studies in accordance with the Guidelines for Good Pharmacoepidemiology Practice (GPP), Good Practice of Secondary Data Analysis (GPS), Good Epidemiological Practice (GEP) as well as the ENCePP Guide on Methodological Standards in Pharmacoepidemiology with the ENCePP Guide on Methodological Standards in Pharmacoepidemiology and the ENCePP Code of Conduct (www.encepp.eu). Standard operating procedures, work instructions and checklists are used to guide the conduct of a study. These procedures and documents include rules for secure and confidential data storage, methods to maintain and archive project documents, rules and procedures for execution and quality control of SAS programming, standards for writing protocols and reports, and requirements for senior scientific review of key study documents.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This study will use real-world data to evaluate safety concerns and collect long-term data on NOCDURNA in three European countries: Denmark, Germany and Sweden. The selected countries are deemed to have a satisfactory number of patients exposed to NOCDURNA and longitudinal databases/registries are available in these countries with information required to meet the study objectives. Overall, the quality of data, including completeness of study variables and coverage, is considered high for the data sources to be used. Nevertheless, there are limitations to consider.

9.9.1 Definition of primary outcome

The ICD-10 diagnosis code (E87.1) used to define the primary outcome of the study, hyponatraemia, encompasses both hypo-osmolality and hyponatraemia, though hyponatraemia is recognised as the most common electrolyte disorder. Therefore, it may be possible that the incidence of hyponatremia is overestimated. On the other hand, the diagnosis code is expected to be underutilised in clinical practice, leading to underestimation of the incidence of hyponatraemia. This underestimation is not expected to differ between the NOCDURNA cohort and the LUTS cohort, although it cannot be ruled out that misclassification of the outcome may be differential. Consequently, the estimation of the IRR of hyponatraemia could be impacted.

9.9.2 Data sources

In Denmark and Sweden, the patient registries used do not cover diagnoses made in primary care; therefore, not all diagnoses will be captured. The outcomes of interest are, however, diagnosed in specialist care and are anticipated to be fully captured in the study.

In the German GePaRD, it will not be possible to follow patients who are no longer covered by or change their statutory health insurance provider contributing information to the database. However, membership in GePaRD is very stable. Therefore, misclassification (underestimation) of outcomes will be minimal in both the NOCDURNA and LUTS cohorts. A prescription for NOCDURNA could also be misclassified as being the first-ever although it is prevalent. The same patient could thus be included twice in the study leading to double-counting of the patient.

Information on cause-specific death will only be available in Denmark and Sweden. This means that the study objectives as they relate to death from CVD, VTE events and heart failure will not be possible to evaluate in the German GePaRD.

Information on hospital intensive care will only be available for Sweden and laboratory data only for part of Denmark. Consequently, there will be limited data to address the study objectives relating to hyponatraemia requiring hospital intensive care and clinically significant hyponatraemia, respectively.

Further limitations are related to the use of prescription data. Although the prescription registries used to ascertain exposure information in Denmark and Sweden have full

coverage of dispensed drugs from community pharmacies, drugs provided in hospitals or institutions are largely not included. GePaRD covers all reimbursable dispensed drugs in the outpatient setting, e.g. also in nursing homes, but does not capture dispensations of drugs during the hospital stay of a patient. This limitation, however, is not expected to influence the cohort and exposure definitions, as the medical conditions of interest are treated in outpatient care and NOCDURNA is by large dispensed from community pharmacies.

Exposure information will be obtained from dispensed prescriptions. As the prescribed or used dose or information on discontinuation of drugs use is not available in the data sources to be used, the on- and off-treatment episodes of NOCDURNA will be calculated based on the recommended daily dosage and a pre-defined permissible gap between dispensations. It will also be assumed that each oral lyophilisate is consumed, possibly resulting in misclassification (overestimation) of exposure to NOCDURNA. Thus, the robustness of the definitions for on- and off-treatment episodes of NOCDURNA will be investigated in sensitivity analyses.

9.9.3 Definition of the NOCDURNA cohort

There is no specific diagnosis code for idiopathic nocturnal polyuria, which is the indication for NOCDURNA. Instead the present study will include all patients that are treated with NOCDURNA (irrespective of underlying disease). This approach will give a broad and comprehensive assessment of the safety of NOCDURNA. All study objectives will, however, be evaluated among patients with a diagnosis of polyuria at the time of their first NOCDURNA prescription.

9.9.4 Data analysis

Despite adjusting the comparative analyses for several important potential confounders, residual confounding may remain. The data sources to be used do not include information on possible confounders related to disease status and severity, behaviour, lifestyle, family history or variation in healthcare delivery. Also, residual confounding may remain related to, for example, incomplete recording of diagnoses in the data sources.

Heterogeneity is anticipated in the meta-analyses combining the results from the three countries. Potential heterogeneity in the results from the countries will be addressed by using a random-effects model.

9.10 OTHER ASPECTS

Strengths of the research methods:

A retrospective design of this study will reflect how patients are handled in real-world clinical practice and hence provide a meaningful evaluation of the risks associated with NOCDURNA use. Furthermore, using real-world retrospective data does not impose a promotional effect and interfere with prescribing patterns of NOCDURNA. Additionally, as

the study will be based on large databases and administrative (national) healthcare registries, it will generate a relatively large sample size, which is likely to be required to identify safety issues related to NOCDURNA in the real-world setting. Nevertheless, the study and its power depend on the uptake of NOCDURNA in routine clinical practice and any assumptions regarding sample size are therefore uncertain.

The present study will provide data on the safety of NOCDURNA in the total population and specifically in elderly patients. The relatively long follow-up period will allow for the assessment of longer-term safety concerns such as cardiovascular and thromboembolic events. The use of a comparator cohort (LUTS patients) will enable meaningful comparisons of the safety risks associated with the treatment with NOCDURNA.

10 PROTECTION OF HUMAN SUBJECTS

10.1 RESPONSIBILITIES OF SPONSOR/ SPONSOR REPRESENTATIVE

Sponsor

Ferring is responsible for reviewing of the protocol, reviewing and refining of statistical analysis plan, development of definitions for key events of interest, development of timelines for analysis, authorship of Executive Summary to accompany trial results, reviewing of publications derived from study results.

Sponsor representative

The sponsor representative is responsible for the conduct of the study in accordance with local regulations and guidelines. The sponsor representative will also be responsible for writing most of the protocol, statistical analysis plan, ethics application, paperwork related to data extraction, and for carrying out data extraction, data analysis and report writing.

10.2 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

This study is a registry trial, and the analysis is based on secondary data use. All data directly accessed by the sponsor representative will be pseudonymised. According to applicable legislation in each country, informed consent from research study participants is not required for analyses of de-identified secondary data from existing databases without any direct enrolment of individuals.

This study will be conducted in accordance with applicable laws and regulations of the region, country or countries where the study is being conducted, as appropriate.

In Denmark, access to data will be applied for from the Danish Health Data Authority and Statistics Denmark.

In Germany, BIPS will apply for project-specific permits from the SHI providers. Once approval has been granted, the SHI provider seeks official project approval from the governing authority.

In Sweden, an application will be submitted for approval to the Swedish Ethical Review Authority. Such an approval from is required to access the data from the Swedish data holders.

10.2.1 Ethical principles

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices, including but not limited to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, the ENCePP Code of Conduct, and the Guidelines for GPP of the ISPE.

All necessary regulatory submissions (e.g., Institutional Review Board/Ethics Committee) will be performed in accordance with local regulations including local data protection regulations (also see section 9.6).

10.2.2 Data protection

All data processing as part of the present study will be done in compliance with all locally applicable laws and regulations, as well as in compliance with the EU General Data Protection Regulation (GDPR).

10.2.3 Record retention

The sponsor representative will retain all study records and source documents in accordance with internal operating procedures, or as long as required by the regulatory authorities. Any patient-level data accessed by the sponsor representative will be stored in safe IT environments.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The present study will be based on the secondary use of data that has already been collected for other purposes. Thus, according to the European Medicines Agency (EMA) Good Pharmacovigilance Practices (GVP) Module VI, the submission of suspected adverse reactions in the form of individual case safety reports is not required. All adverse events/reactions collected for the study will be recorded and summarized in the interim safety analysis and in the final study report.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Based on the study report, the sponsor, sponsor representative and possible other contributors may prepare a scientific manuscript(s) for academic publication. The sponsor, sponsor representative and possible other contributors decide the publication forums.

The sponsor, sponsor representative and possible other contributors are committed to ensuring that authorship for all publications should comply with the criteria defined by the International Committee of Medical Journal Editors, ICMJE.

Within 3 months following the study report, an abstract of the study findings will be made available to the public through the EU PAS register. The main results of the study will be published, whether positive or negative, including results from a possibly prematurely terminated study. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests.

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ANNEXES

Annex 1 List of stand-alone documents

Number	Date	Title
1	11 January 2019	Summary of NOCDURNA extended feasibility study
2	21 June 2019	ENCePP Checklist for Study Protocols

Annex 2 ENCePP checklist for study protocols

A copy of the ENCePP Checklist for Study protocols was downloaded from http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml, completed and signed by the main author of the study protocol. It is available as a standalone document.

Annex 3 Definitions of the LUTS cohort, outcome events and covariates

Table A1. ATC codes used to define the LUTS cohort

Characteristic	ATC code	Description
Overactive bladder	G04BD	Drugs for urinary frequency and incontinence
Benign prostatic hyperplasia	G04C	Drugs used in benign prostatic hypertrophy

Table A2. Codes used to define subpopulations of interest

Characteristic	ICD-10 code	ATC code	Description
Hyponatraemia	E87.1		
Polydipsia	R63.1		
Loop diuretics		C03C	
Glucocorticosteroids		H02AB	
Congestive heart failure	I50.2		Systolic (congestive) heart failure
	I50.3		Diastolic (congestive) heart failure
	I50.4		Combined systolic (congestive) and diastolic (congestive) heart failure
Chronic kidney disease	N18.3		Chronic kidney disease, stage 3 (moderate)
	N18.4		Chronic kidney disease, stage 4 (severe)
	N18.5		Chronic kidney disease, stage 5
	N18.6		End stage renal disease
Syndrome of inappropriate antidiuretic hormone secretion	E22.2		
Uncontrolled hypertension	I16		Hypertensive crisis
	I67.9		Hypertensive encelopathy
Coagulation disorders	D68.0		Von Willebrand's disease
	D68.5		Primary thrombophilia
	D68.6		Other thrombophilia

Table A3. Codes used to define outcome events

Outcome	ICD-10 code	Description
Hyponatremia		
Hyponatraemia	E87.1	
Hyponatremia (biochemical definition)	n/a	Will be ascertained using biochemical definition: serum sodium concentration <135 mmol/L (mild hyponatraemia) *Evaluated only in Denmark*
Major cardiovascular events (MACE)		
Myocardial infarction	I21, I22	
Stroke, ischemic	I63.3-I63.9, I66	
Major venous thromboembolic events		
Pulmonary embolism	I26	
Deep vein thrombosis	I80.1–I80.9	
Portal vein thrombosis	I81	
Mortality		
All-cause mortality	Any	Death from any cause
Heart failure		
Heart failure	I50	

Table A4. Codes used to define covariates

Covariate	ICD-10 code	ATC code	Description/comment
Comorbidities			
History of hyponatraemia, MACE and VTE	Please refer to Table A1		
Polyuria	R35		Polyuria
Diabetes mellitus	E10		Type 1 diabetes mellitus
	E11		Type 2 diabetes mellitus
	E12		Malnutrition-related diabetes mellitus
	E13		Other specified diabetes mellitus
	E14		Unspecified diabetes mellitus
Diabetes insipidus	E23.2		
Overactive bladder	N31.0		Uninhibited neuropathic bladder, not elsewhere classified
	N31.2		Flaccid neuropathic bladder, not elsewhere classified
	N31.9		Neuromuscular dysfunction of bladder, unspecified
	N39.4		Other specified urinary incontinence
	R39.1		Other difficulties with micturition
		G04BD	Drugs for urinary frequency and incontinence
Benign prostatic hyperplasia	N40		Benign prostatic hyperplasia
	D29.1		Benign neoplasm of prostate
		G04C	Drugs used in benign prostatic hypertrophy
Urinary tract infection	N39.0		Urinary tract infection, site not specified
	N30		Cystitis
	N10		Acute tubulo-interstitial nephritis
Polydipsia	R36.1		Excessive thirst
Heart failure	I50		
Hypertension	I10		Essential (primary) hypertension; medications to be used as proxy (see below under co-medications)
Hyperlipidaemia	E78		Disorders of lipoprotein metabolism and other lipidaemias; medications to be used as proxy (see below under co-medications)
Atrial fibrillation	I48		
Obesity	E66		
Kidney disease	N18		
	N19		
Cystic fibrosis	E84		
Pre-eclampsia	O11		Pre-eclampsia superimposed on chronic hypertension
	O14		Pre-eclampsia

Covariate	ICD-10 code	ATC code	Description/comment
Chronic lung disease	J40-J47		Chronic lower respiratory diseases
	J60-J70		Lung diseases due to external agents
	J80		Adult respiratory distress syndrome
	J82		Pulmonary eosinophilia, not elsewhere classified
	J84		Other interstitial pulmonary diseases
	J95-J99		Other diseases of the respiratory system
Liver disease	K70-K77		Diseases of liver
	F10		F10 (mental and behavioural disorders due to use of alcohol) and N07BB (drugs used in alcohol dependence) included as proxy measures of liver disease
		N07BB	
Cancer	C00-C43		Cancer excluding non-melanoma skin cancer C61 (prostate cancer) and C67 (bladder cancer) of special interest
	C45-C97		
Dementia	F00		Dementia in Alzheimer disease
	F01		Vascular dementia
	F02		Dementia in other diseases classified elsewhere
	F03		Unspecified dementia
	F04		Organic amnesic syndrome, not induced by alcohol and other psychoactive substances
	G30		Alzheimer's disease
	G31.0		Frontotemporal dementia
	G31.1		Senile degeneration of the brain
Number of hospitalisations	Any		Marker of overall health; to be assessed in the year before the index date
Number of emergency room visits	Any		Marker of overall health; to be assessed in the year before the index date
Co-medications, including drugs that may increase the risk of hyponatraemia			
Loperamide		A07DA03	
Antidiabetics		A10	A10BB (sulfonylureas including chlorpropamide), of special interest
Amiodarone		C01BD01	
Antihypertensives		C02	
Diuretics		C03	C03A, C03B, C03C, C03D and C03E of special interest
Beta blocking agents		C07	C07B, C07C and C07D of special interest

Covariate	ICD-10 code	ATC code	Description/comment
Calcium channel blockers and diuretics		C08G	
ACE inhibitors		C09A	C09BA of special interest
Angiotensin II receptor blockers		C09C	
Angiotensin II receptor blockers (combinations)		C09D	C09DA of special interest
Lipid-modifying agents		C10	
Vasopressin and analogues (incl. desmopressin)		H01BA	
Systemic corticosteroids		H02	
Antiepileptics		N03A	N03AF01 (carbamazepine) and N03AX09 (lamotrigine) of special interest
Non-selective monoamine reuptake inhibitors		N06AA	
Selective serotonin reuptake inhibitors		N06AB	
Chlorpromazine		N05AA01	
NSAIDs		M01A	
Opioids		N02A	
Phenothiazines with aliphatic side-chain		N05AA	N05AA01 (chlorpromazine) of special interest
Lithium		N05AN01	
Antidepressants		N06A	
Antiinflammatory agents, non-steroids		M01A	

STATISTICAL ANALYSIS PLAN

POST AUTHORISATION SAFETY STUDY (PASS), SAP

Post-authorisation safety study of NOCDURNA for the symptomatic treatment of nocturia due to idiopathic nocturnal polyuria: A multi-country cohort study using secondary data

000248

Investigational Product: Desmopressin, one oral lyophilisate per day

Indication: N/A

Phase: IV

Author: PPD

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Change log

Version No.	Effective Date	Reason for the Change / Revision	Supersedes

Review and Approval of Statistical Analysis Plan

Author:

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Reviewers:

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Approval by (e-signed in REAL):

PPD

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1 INTRODUCTION

This document describes the planned statistical analyses for 000248, Post-authorisation safety study of Nocdurna ® for the symptomatic treatment of nocturia due to idiopathic nocturnal polyuria: A multi-country cohort study using secondary data.

Please observe that this is NOT a clinical study but a retrospective study.

1.1 Definitions/ Abbreviations

1.1.1 Definition of Terms

Terms	Definitions
Hyponatraemia	**Low sodium in the blood**
Lyophilisate	**A tablet that dissolves in the mouth**

1.1.2 Abbreviations

Abbreviations	Meaning of abbreviations in document
AE	**Adverse Event**
ATC	**Anatomic Therapeutic Chemical**
CHF	**Acute exacerbation of congestive heart failure**
GDPR	**General Data Protection Regulation**
GePaRD	**German Pharmacoepidemiological Research Database**
ICD 10	**International Statistical Classification of Diseases and Related Health Problems - Tenth Revision, the system used in health care to classify diseases**
IR	**incidence rate**
IRR	**incidence rate ratios**
IQR	**interquartile range**
MACE	**Major adverse cardiovascular events**
SmPC	**Summary of Product Characteristics**
SAP	**Statistical Analysis Plan**
SIR	**Swedish Intensive Care Registry**
VTE	**Major venous thromboembolic event**

1.2 Presentation of Results

1.2.1 Presentation of Descriptive Results

Categorical data will be summarised, unless otherwise stated, using frequency (n) and relative frequencies as percentage (i.e. n/N*100).

Continuous data will be presented for observed values using the number of subjects (N), mean and standard deviation (SD), median and interquartile range (IQR), and range (minimum to maximum) and number of patients with missing values. The distribution of continuous variables (age and exposure time) will also be examined graphically using boxplots, symmetry plots, normal quantile plots and normal probability plots.

Table shells for all categorical and continuous variables are shown in Section 14. The descriptive tables will be divided by Nocdurna ® /LUTS and by gender, then repeated for patients above or equal 65 years. Some tables will be stratified for events during the first month and later.

1.2.2 Presentation of Inferential Results

Frequentist inferential results will be presented using the respective point estimates, their Standard Errors and two-sided 95% confidence intervals unless otherwise stated.

Table shells per type of analysis and standard figures are also provided in section 14 and for the meta-analysis and the interpretation it is important that the table shells are followed. The figures in the 2021 report are not expected to be completely harmonized because the data from the different countries will be variable making a fix determination of the axis scale is difficult prior to reviewing the data.

1.2.3 Subject Data Listings by Domain

Subject data will not be listed due to the large volume of data (estimated approximately 300,000 patients in three countries) and it would also be a violation of data privacy rules. Individual subject data are not to be disclosed under any conditions.

2 TRIAL OBJECTIVES AND ENDPOINTS

The overall objective of the present study is to increase the understanding of the long-term safety of Nocdurna ® (desmopressin) as used in routine clinical practice. This will be achieved by assessing the incidence risk and rate of hyponatraemia, cardiovascular (including acute exacerbation of congestive heart failure in patients with chronic cardiac insufficiency) and thromboembolic events among patients, in particular the elderly, treated with Nocdurna ®. The findings will be put into context by also analysing a population with lower urinary tract symptoms (LUTS) using the drugs defining the LUTS population and with no usage of Nocdurna ®. This LUTS population should also be new users of the LUTS drugs, just like the Nocdurna ® population.

Estimated incidence rates among Nocdurna ® patients will be compared with incidence rates among a cohort of patients with newly initiated treatment for LUTS for events as listed below.

The **primary objective** is to:

Estimate the incidence rate of symptomatic hyponatraemia (defined as a recorded diagnosis of hyponatraemia) among patients treated with Nocdurna ®, and patients with LUTS separately, overall and by subgroups (elderly patients aged ≥65 years, patients with and without contraindications).

The **secondary objectives** are to:

1. Describe the demographic and health characteristics of the population receiving Nocdurna ® and patients with LUTS, including prevalence of risk factors for outcomes of interest as specified in Table 10

2. Estimate the incidence rate of hyponatraemia requiring hospital intensive care among patients treated with Nocdurna ® and patients with LUTS separately.

3. Estimate the incidence rate of clinically significant hyponatraemia (defined as a serum sodium concentration of <130 mmol/L) among patients treated with Nocdurna ® and patients with LUTS separately.

4. Estimate the rate of all-cause mortality among patients treated with Nocdurna ® and patients with LUTS separately.

5. Estimate the incidence rate of the following events of special interest among patients treated with Nocdurna ® and patients with LUTS separately:

    a. Major cardiovascular events (composite endpoint)

    b. Major venous thromboembolic events (composite endpoint)

6. Estimate the incidence rate of acute exacerbation of congestive heart failure among patients who have chronic cardiac insufficiency/heart failure treated with Nocdurna ®, and patients with LUTS, separately.

7. In addition, a subgroup analysis of all patients adhering to the label as assessed by the proxy based on diagnosis and contra-indications (as available) will be conducted.

8. Estimate the incidence rate of primary and secondary outcomes of interest between patients treated with Nocdurna ® compared to a population of LUTS patients adjusted for confounding factors (age class and gender), by country where data is available.

9. Estimate the incidence rate of cardiovascular and thromboembolic events of interest resulting in treatment withdrawal of Nocdurna ®.

All secondary objectives will be evaluated in the overall population and among subgroups (elderly patients aged ≥65 years, patients with and without contraindications).

2.1 Outcomes

The primary and secondary outcomes presented below are also summarized in Table 1.

2.1.1 Primary outcome

The primary outcome is symptomatic hyponatraemia, as defined by a primary or secondary diagnosis of hyponatraemia (ICD-10 code: E87.1) recorded in Sweden and Denmark, and by a discharge diagnosis in the German Pharmacoepidemiological Research Database (GePaRD). Thus, diagnoses from within hospital inpatient and specialist outpatient care will be considered in the Swedish and Danish data sources. Primary and secondary diagnoses of hyponatraemia will be considered equally important in the Swedish and Danish data sources. In the German GePaRD, the focus will be on discharge diagnoses, which are inpatient (not outpatient) diagnoses and in this way outcomes will be assessed based on hospital data in Germany.

An incident event is defined as the first record of symptomatic hyponatraemia during each patient's follow-up. The incidence rate of the primary outcome will be modelled using Poisson regression. If recurrent events of symptomatic hyponatremia have been observed, a Cox model for recurrent events may be applied. If the Poisson regression fails to converge, the unadjusted rate will be presented instead as seen in Table **9** in the row with 'Mean unadjusted rate of events (events/1000 person-years)'.

2.1.2 Secondary outcomes

The secondary outcomes for this study are the following events:

1. Hyponatraemia requiring hospital intensive care, defined as a primary or secondary diagnosis of hyponatraemia (ICD-10: E87.1) recorded in an intensive care unit.

This outcome will only be evaluated in Sweden using data collected from the Swedish Intensive Care Registry (SIR), as information to distinguish between hospital inpatient care in general and intensive care in particular is not available in the Danish national registries or the German GePaRD.

Only incident events (first hyponatraemia record from within hospital intensive care during follow-up) will be considered.

2. Clinically significant hyponatraemia, defined as a serum sodium concentration of <130 mmol/L.

In addition, hyponatraemia by level of severity will be evaluated, where *mild* hyponatraemia is defined as a serum sodium concentration of above 130 to less than 135 mmol/L, *moderate* as a serum sodium concentration of above 125 to less than 130 mmol/L, and *severe* as a serum sodium concentration of less than or equal 125 mmol/L.

The Danish National Laboratory Database Research Table will be used to evaluate the level of severity using actual measurements of plasma sodium levels. The evaluation of this outcome will be restricted to patients residing in the four Danish regions covered by the database.

Incident and recurrent events will be considered and analysed separately.

3. All-cause mortality, defined as death from any cause.

This outcome can be evaluated in all data sources: in Denmark and Sweden using the national cause of death registries, and in Germany will BIPS identify death and date of death using a database-specific algorithm taking into consideration discharge from hospital due to death and end of insurance due to death. .

4. Major adverse cardiovascular events (MACE), defined as a record of myocardial infarction or stroke, (see Table 72 for a list of diagnosis codes used to define these conditions) recorded in each relevant country data source. In Sweden and Denmark, fatal events of myocardial infarction or stroke are also considered as MACE (as cause of death is available). MACE is a composite endpoint.

In addition to overall MACE events, MACE requiring hospital intensive care defined as a primary or secondary diagnosis of MACE recorded in a hospital intensive care unit (ICU) will be reported in Sweden.

5. Major venous thromboembolic (VTE) events, defined as a record of a deep vein thrombosis, pulmonary embolism or portal vein thrombosis (see Table 72, for a list of diagnosis codes used to define these conditions) recorded in each relevant country data source. In Sweden

and Denmark, fatal events of VTE are also considered (as cause of death is available). VTE is a composite endpoint.

In addition to overall VTE events, VTE events requiring hospital intensive care defined as a primary or secondary diagnosis of VTE events recorded in a hospital intensive care unit (ICU) will be reported in Sweden.

Fatal and non-fatal MACE and VTE events will be assessed separately in Denmark and Sweden. Fatal events will only be assessed in Denmark and Sweden using the national registries. Information on cause of death is not available in the German GePaRD unless the patient is dying in the hospital, but German data will not be included in the analysis. For fatal events, death from a MACE or VTE event recorded as the underlying or contributory cause will be considered. For non-fatal MACE and VTE events, primary and secondary diagnoses will be considered equally important (in Germany: discharge diagnoses). Incident events of MACE and VTE in the study time period will be analysed.

6. Acute exacerbation of congestive heart failure.

Given that cardiac insufficiency is a contraindication for the use of Nocdurna ®, the incidence of acute exacerbation of congestive heart failure among patients who have chronic cardiac insufficiency is considered an exploratory outcome in this study.

The outcome will only be analysed among patients with prevalent chronic heart failure. Prevalent chronic heart failure will be defined as ever having had a primary or secondary diagnosis of heart failure (ICD-10: I50; in German GePaRD: outpatient or inpatient diagnosis) before the index date, but no recorded primary diagnosis of heart failure from hospital inpatient care or the acute and emergency ward in the 6 months prior to the index date (German GePaRD: discharge diagnoses). Among these patients, acute exacerbation of heart failure will be defined as a primary diagnosis of acute or acute-on chronic heart failure from hospital inpatient care or the acute and emergency ward, or death from heart failure as the underlying or contributory cause, see Figure 2 for a simple description. Non-fatal events of acute exacerbation of heart failure will be evaluated in all three countries, while fatal events will only be evaluated in Denmark and Sweden.

In addition, a subgroup analysis of all patients adhering to the label as assessed by the proxy based on diagnosis and contra-indications (as available) will be conducted.

7. MACE and VTE events resulting in treatment withdrawal of Nocdurna ® in Sweden.

Serious events resulting in treatment withdrawal of Nocdurna ® will be evaluated in the Nocdurna ® exposed group only in Sweden. Treatment cessation of Nocdurna ®, defined by a time after prescription longer than the permissible gap, will be defined as the end of an on-treatment period. Serious events will be evaluated in 14 days prior to the treatment cessation date.

Serious MACE and VTE events will be defined as a primary or secondary diagnosis of MACE or VTE recorded in a hospital intensive care unit. This can only be evaluated in Sweden.

Table 1. Definitions of primary and secondary outcome variables

Variable	Definition	Countries in which outcome assessed
Primary outcome		
Symptomatic hyponatraemia	Primary or secondary diagnosis of hyponatraemia (E87.1)	**Denmark, Germany (hospital discharge diagnosis for in-patient hospitalization), Sweden**
Secondary outcomes		
Hyponatraemia requiring hospital intensive care	Primary or secondary diagnosis of hyponatraemia (E87.1) from hospital intensive care	Sweden
Clinically significant hyponatraemia including hyponatraemia by severity	Serum sodium concentration <130 mmol/L Mild hyponatraemia: serum sodium concentration 130 to<135 mmol/L Moderate hyponatraemia: serum sodium concentration above 125 to<130 mmol/L Severe hyponatraemia: serum sodium concentration ≤125 mmol/L	Denmark
All-cause mortality	Death from any cause	**Denmark, Sweden, Germany**
Major cardiovascular events	Primary or secondary diagnosis of cardiovascular death (underlying or contributory cause), myocardial infarction or stroke	**Denmark, Germany (non-fatal events only; discharge diagnosis for in-patient hospitalization)** **Sweden**
Major venous thromboembolic events	Primary or secondary diagnosis of deep vein thrombosis, pulmonary embolism, portal vein thrombosis, *or* death from either of these conditions as the underlying or contributory cause	**Denmark** **Germany (non-fatal events only; discharge diagnosis for in-patient hospitalization)** **Sweden**
Acute exacerbation of congestive heart failure	Primary diagnosis of acute or acute-on-chronic heart failure from hospital inpatient care or the acute and emergency ward, or death from heart failure as the underlying or contributory cause	**Denmark** **Germany (non-fatal events only; discharge diagnosis for in-patient hospitalization)** **Sweden**
Serious adverse events	Primary or secondary diagnosis of MACE or VTE leading to admission to a hospital intensive care unit	Sweden

3 TRIAL DESIGN

3.1 General Design Considerations

This is a multi-country, cohort study using secondary data collected from research databases and administrative national healthcare registries in selected European countries (Denmark, Germany, and Sweden).

Cohorts of patients using Nocdurna ® or treatment of LUTS (new user) will be identified from existing data sources in each country of study. These data sources hold information on dispensed prescriptions, patient demographics and diagnoses. The LUTS contextual cohort will be comprised of patients based newly starting treatments associated with polyuria, receiving relevant standard care. For secondary comparative analyses, the comparator group for Nocdurna ® patients will be LUTS patients.

The study period will be from the date of launch of Nocdurna ® until the date of latest data availability in each country, considering that the final study report is planned for 2023. Given the lag time of data updates and time allocated for analysis and reporting, last data included in the final report is likely to be up to end of 2021. Historical data, reflecting a minimum of 12 months before initiation of treatment with Nocdurna ® (or initiation of treatment for LUTS), will be used to assess characteristics (e.g., demographics, indication, comorbidities, and co-medication) at the index date.

In addition to the final study report, there will be 2 interims reports (in 2021 and 2022) on study progress and any emerging safety data. The final report will include meta-analysis for combining the safety in the three countries.

3.1.1 Sample Size

The study will be conducted among patients using Nocdurna ® in the outpatient setting in three European countries: Denmark, Germany and Sweden. These countries have been selected following careful consideration of multiple factors: a feasibility assessment of the ability of candidate data sources to address the study objectives, recommendations by the Swedish Medical Products Agency (MPA), and expected uptake of Nocdurna ® in the candidate countries. Sales data was used as an indicator of uptake of Nocdurna ® to ensure a sufficiently large exposed population as shown in Table 2. Based on the information contained in the data sources available in the candidate countries and the estimated extent of exposure to Nocdurna ® based on available sales data in European countries, Denmark, Germany and Sweden were chosen as countries of study.

Table 2. Nocdurna ® sales statistics (2018) and launch dates in candidate countries of study

Country	**Share of Nocdurna ® sales in 2018 (%)**	**Nocdurna ® commercial launch date**
Germany	40	January 2017
United Kingdom	22	November 2016
Belgium	9	March 2017
The Netherlands	7	November 2016
Sweden	7	January 2017
Denmark	5	August 2017

The study will use data from countries where the uptake of Nocdurna ® is expected to provide a sufficiently large population of exposed patients. Therefore, the sampling frame has been constructed using the distribution of sales data in the EU.

3.1.2 Sample size for primary outcome analysis

All available patients with a Nocdurna ® prescription in the study period will be included in this study. The primary objective is descriptive.

In addition to the feasibility study detailed above, Nocdurna ® sales data was reviewed to estimate the available number of patients. Table 3 shows the patient estimate based on the share of Nocdurna ® sales in 2018, the number of oral lyophilisates, 50% adherence, and coverage of the database per country of this study. GePaRD coverage is approximately 18% of the German population.

Table 3. Patient estimate for 2018 per country

Country	**Share of Nocdurna ® sales in 2018 (%)**	**Number of** oral lyophilisates	**Patient estimate assuming 50% adherence**	**Patient estimate from the Database**
Germany	40	661.950	3.678	662
Sweden	7	117.250	651	651
Denmark	5	82.260	457	457

The patient estimate for Sweden is thus in line with the results from the feasibility study. The coverage and availability of data from Denmark is comparable to Sweden, as both data sources rely on national registers.

Extrapolating the patient estimated from Table 3 to a time period 2018-2021 (end of the study time period), and assuming conservatively that sales remain constant during the time period, the number of Nocdurna ® patients in this study will likely be at least:

- Germany (GePaRD): 2650
- Sweden: 2610
- Denmark: 1830

However, the secondary objective 6 with a sub-population with chronic cardiac insufficiency demands for the analysis of a much smaller sample size and with an even smaller number of events. During the analysis and interpretation of the results these facts must be considered.
Since the primary objective in the study is descriptive, no formal sample size has been calculated and this also implies that no statistical hypothesis has been formulated. Calculated p-values are also descriptive.

3.1.2.1 LUTS patients

All the above calculations are only referring to the Nocdurna ® treatment. For the LUTS patients the MEDSTAT.DK database has been used to calculate the number of patients. In 2017 there were 82,035 patients using the diagnose code G04C and 45,270 patients using the ATC code G04BD, a sum with a maximum of 127,305 patients, since some patients could have both drugs. Extrapolating to the study period a sum of approximately 300,000 patients in the LUTS group should be expected. In Sweden the patient number should be a factor 1.7 larger and in Germany a factor 2.3 larger than the patient number in Denmark, while taking the country populations in Sweden into account and the population in Germany and the coverage of the GePaRD database.

3.1.3 Trial Stages

N/A

3.1.4 Trial Epochs

N/A

3.1.5 Visits [and Visit Windows]

There are no planned visits in this study. The patients will be followed through the registries.

The planned study period ranges from the date of launch of Nocdurna ® (Table 2) to the date of latest data availability in each country. Thus, the planned study periods are as follows:

- Denmark: 29 August 2016 to 31 December 2021
- Germany: 1 January 2017 to 31 December 2021

- Sweden: 20 January 2017 to 31 December 2021

Historical data, reflecting a minimum of 12 months before index date will be used to assess baseline characteristics (e.g., demographics, comorbidities and co-medications). Thus, the total period for which data will be collected is from at least 12 months before the date of launch of Nocdurna ® to the date of latest data availability in each country.

4 PROTOCOL VIOLATIONS

There are no exclusion criteria. Patients that are identified as valid cases will be followed until end-of-study.

5 ANALYSIS SETS

5.1 Cohort entry

Cohort entry is defined by the index date.

5.1.1 Index date - Nocdurna ® cohort

The index date is defined by their first ever prescription of Nocdurna ® in the study period.

5.1.2 Index date - LUTS cohort

The index date is defined by their first ever prescription of medication used to treat urinary frequency and incontinence (Anatomic Therapeutic Chemical (ATC) codes G04BD) or benign prostatic hypertrophy (ATC codes G04C) in the study time period.

5.1.3 Cohort exit

Right censoring events – Nocdurna ® cohort

Patients will be followed from the index date to the date of a censoring event: a dispensed prescription for a vasopressin agonist or desmopressin drug other than Nocdurna ®, transfer out of the database, emigration, death or end of the study period, whichever occurs first and irrespective of treatment status (on/off drug). As appropriate, patient will also be followed from index date to the date of the diagnosis of the outcome of interest, or end of treatment of Nocdurna ®.

Right censoring events – LUTS cohort

Patients will be followed from the index date to the date of the censoring event: a dispensed prescription for a vasopressin agonist or desmopressin drug, transfer out of the database, emigration, death or end of the study period, whichever occurs first. As appropriate, patient will also be followed from index date to the date of the diagnosis of the outcome of interest, or the end of treatment of drugs defining the LUTS cohort.

5.1.4 Eligibility criteria

Inclusion criteria – Nocdurna ® cohort

The cohort of Nocdurna ® patients will consist of individuals meeting the following inclusion criteria:

- A first-ever dispensed prescription for Nocdurna ® [desmopressin; Anatomical Therapeutic Chemical (ATC) code: H01BA02; brand name: Nocdurna ®; dose: 25 or 50 micrograms] recorded in the relevant country-specific data source between its launch date and the latest date of data availability in each country. The first-ever dispensation is in the German database, the first dispensation covered by their insurance databases, since patients could

move between different database providers and the first detected dispensation might not be the first-ever.

Note: To identify Nocdurna ® dispensations, first all desmopressin dispensations with the ATC code H01BA02 will be extracted, then the cohort for analysis will be selected using the brand name Nocdurna ® and the dose of Nocdurna ® (25 or 50 microgram).

- Aged 18 years and above on the index date.
- At least 12 months' registration in the relevant country-specific database(s) prior to the index date, to ensure a sufficiently long period of baseline data availability.

5.1.5 Exclusion criteria – Nocdurna ® cohort

The following exclusion criteria will be applied to the Nocdurna ® cohort:

- Treatment with vasopressin or any of its analogues (defined as a dispensed prescription within 6 months (180 days) before the index date [index date -1 day]; ATC codes H01BA), irrespective of formulation or dose/strength.
- Multiple desmopressin drugs dispensed on the index date.
- Patients with missing information on the variables required for the (key) analyses (i.e. missing information on age and sex) will be excluded.

5.1.6 Inclusion criteria – LUTS cohort

Patients meeting the following criteria will be included in the LUTS cohort:

- A first-ever dispensed prescription for a medication used to treat urinary frequency and incontinence (ATC codes G04BD) or benign prostatic hypertrophy (ATC codes G04C) between the launch date of Nocdurna ® and the latest date of data availability in each country. The first-ever dispensation is in the German database, the first dispensation covered by their insurance databases, since patients could move between different database providers and the first detected dispensation might not be the first-ever.
- Aged 18 years and above at index date.
- At least 12 months' registration in the relevant country-specific database(s) prior to the index date, to ensure a sufficiently long period of baseline data availability.

The ATC codes used to define the LUTS cohort are summarized in Table 70.

5.1.7 Exclusion criteria – LUTS cohort

The following exclusion criterion will be applied to the LUTS cohort:

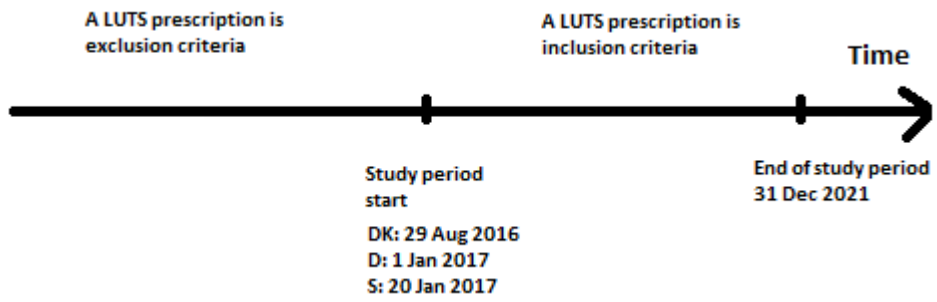
- Treatment with vasopressin or any of its analogues (defined as a dispensed prescription within 6 months (180 days) before the index date [index date -1 day]; ATC codes H01BA), irrespective of formulation or dose/strength.

- If a patient according to the above is qualified for both the Nocdurna ® and the LUTS group, this patient's information must be deleted from the LUTS group, since it is expected that the Nocdurna ® group will be the smallest.

- If a prescription for a LUTS drug is found before the study time period, this patient must be excluded, since the later prescriptions will not be the first ever prescription with in study time period.

- Patients with missing information on the variables required for the (key) analyses (i.e. missing information on age and sex) will be excluded.

Figure 1. Inclusion, exclusion and study period start for LUTS treatment as defined above.



5.2 Full-Analysis Set

N/A

5.3 Per-Protocol Analysis Set

N/A

5.4 Safety Analysis Set

This is a safety study (PASS) and all findings are safety related.

6 TRIAL POPULATION

Patients that are identified according to section 5 will be used as the trial population.

6.1 Demographics and Other Baseline Characteristics

6.1.1 Demographics

Descriptive statistics of baseline demographics variables will be tabulated. The categorical variables will be presented at index date and these are gender, ICD 10 code recorded before or at index date, ATC recorded before or at index date. All available time before index date and at least 12 months are used in the calculation of the ICD 10 and ATC codes. The continuous variables are age at index date, length of exposure, number of hospitalisations before index date, number of emergency room visits before index date. Observe that length of exposure is not a baseline demographic variable, but will be described with the same statistical measures.

6.1.2 Vital Signs at Baseline

N/A.

6.1.3 Physical Examination at Baseline

N/A.

6.1.4 Laboratory Effectiveness/Pharmacodynamical Parameters at Baseline

N/A.

6.1.5 Trial-specific Baseline Variables or History of Disease

N/A.

6.2 Medical History

Medical history will be calculated from the ICD 10 codes recorded in the registries used in the three countries. No MedDRA coding will be done.

7 SUBJECT DISPOSITION

The number of potential patients not included in the study will be summarized. The conditions for not including the patients are; age below 18 years at index date, treatment with vasopressin or any of its analogues defined as a dispensed prescription within 6 months (180 days) and for Nocdurna ® patients and multiple desmopressin drugs dispensed on the index date. It is also important that the LUTS patients is having their first dispensation of a LUTS drug after the launch of Nocdurna ® treatment in the investigated country, so that patients using LUTS before the study start date are excluded. The population with the excluded and included patients will be shown in Table 8.

8 PRIOR AND CONCOMITANT MEDICATION

Prior medication will be tabulated from the specifications in the applications to the ethical boards. Only a limited and targeted number of medications have been specified, since asking for all medication would not be needed for answering the medical objectives in the study and getting information about medication outside the medical scope would be a violation of the privacy rules. Previous medication will be tabulated like shown in Table 10.

9 EXPOSURE AND TREATMENT COMPLIANCE

9.1.1 Extent of Exposure

Exposure person-time will be defined for Nocdurna ® patients from the date of first Nocdurna ® prescription. For comparative analyses, equivalent person-time in the LUTS contextual cohort group will be defined from the index date.

Person-time observed from index date to the date of outcome or censoring event will be determined for both the Nocdurna ® group and the LUTS group.

Estimation of exposure periods: Duration of exposure to the respective study drug (Nocdurna ® or LUTS treatment) will be defined based on the estimated supply of drug dispensations. To estimate the supply, the total drug amount of a dispensation is converted into defined daily doses (DDDs; sex-specific DDD for Nocdurna: 25 µg for females, 50 µg for males). The days supplied added to the dispensation date will approximate the end date of a dispensation.

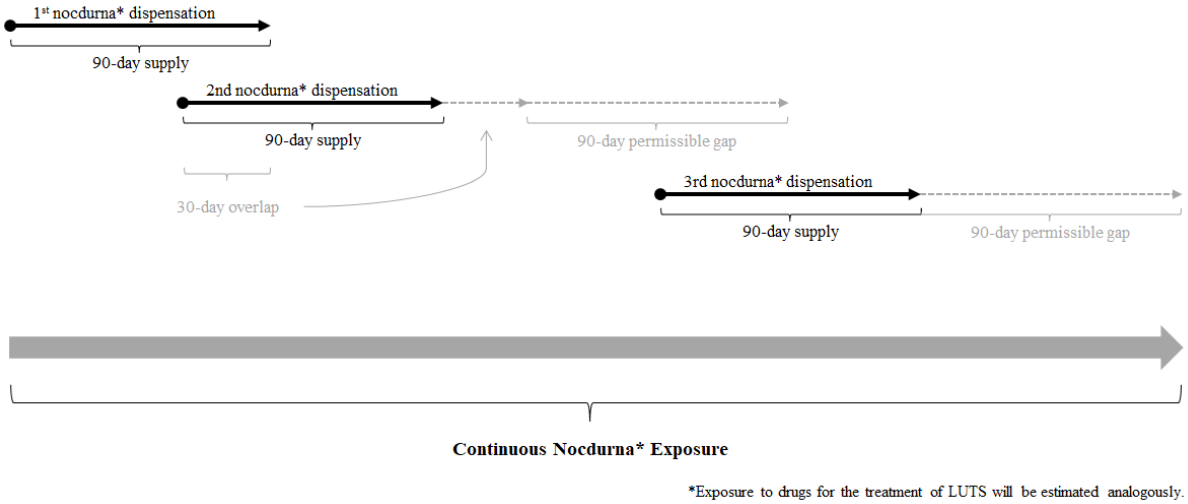
Overlapping dispensations: If a new dispensation of the respective study drug occurs prior to the end date of the previous dispensation, the estimated end date of the latest dispensation will be postponed by the days of overlap.

Permissible gap: If there is a gap after the estimated end date of a dispensation (i.e. there is no new dispensation of the respective study drug covering the first day after the end date of the latest dispensation), the exposure period will be extended. A period equal to the days supplied by the latest dispensation (DDD*1) will be added to the end date of the latest dispensation. In other words, the exposure period continues if a subsequent dispensation occurs within the timeframe of the permissible gap.

End of exposure period: If no subsequent dispensation occurs within the timeframe of a permissible gap, the end of the exposure period will be the last day of the permissible gap.

The above-mentioned considerations apply to both Nocdurna ® and drugs for the treatment of LUTS. For both the Nocdurna ® and LUTS groups, exposure periods start at cohort entry.

There are multiple preparations (multiple ATC codes) defining the treatment of LUTS. All those preparations are considered when defining exposure to LUTS treatment, i.e. concomitant use and switching between different preparations to treat LUTS are allowed within a patient's exposure period. In the Nocdurna ® group, however, only Nocdurna ® dispensations are considered to define exposure periods.



If a person in the Nocdurna group is prescribed desmopressin in a higher dose than in the Nocdurna defining dose (25 or 50 micrograms) the person-time must be stopped when this higher dose is prescribed. Observe that these drug will have the same ATC code as Nocdurna (H01BA02), but another brand name and a higher dose. In Germany the brand will be used to identify Nocdurna.

Treatment restarts following treatment holiday (larger than the permissible gap) will not be evaluated in this study

Observe that if a patient is using the last of the prescribed/dispensed drugs, the end of treatment will be the last day according to the standard dose as defined in section 5.1.4.

On treatment person-time (exposure time) will be tabulated as shown in Table 10 and graphs will be made as shown in Figure 11, Figure 12, Figure 13, and Figure 14.

9.1.2 Treatment Compliance

All dispensed drugs are expected to be taken and no calculations of treatment compliance can be done.

10 SAFETY

General considerations

The present study will be based on the secondary use of data that has already been collected for other purposes. Thus, according to the European Medicines Agency (EMA) Good Pharmacovigilance Practices (GVP) Module VI, (EMA, 2017), the submission of suspected adverse reactions in the form of individual case safety reports is not required. All adverse events/reactions collected for the study will be recorded and summarized in the interim analysis and in the final study report. Since it is not required to collect or submit any safety data for the study, reconciliation is not applicable.

Given between-country differences in the type of data used, governance regulations and patient privacy rules, and expected variations in the background risk of diseases, the countries will be analysed separately and combined in a meta-analysis (where the estimates for each country and cohort will be pooled, as applicable). The meta-analysis will be performed only for the final report which is planned in December 2023.

The distribution of continuous variables (age and exposure time) will be examined graphically using boxplots, symmetry plots, normal quantile plots and normal probability plots as shown in Figure 11, Figure 12, Figure 13, and Figure 14. Exploratory analyses to provide insight into general patterns will be conducted using number and percent within each category with 95% confidence interval (CI) for categorical variables except cohort characteristics, and mean (standard deviation, SD), median (interquartile range, IQR), and other relevant summary statistics for continuous variables. Where/if appropriate, a log transformation of continuous variables (age) will be applied to handle skewness (back-transformed prior to reporting) or a non-parametric approach will be adopted if there is no appropriate transformation. Quantitative variables may be categorised into quartiles as required. These possible back-transformation and quartiles presentation will be judged after the report for the first year 2021 has been completed. These distribution figures is an option for BIPS, who can choose not to produce these figures.

Missing data for covariates will be described. Since missing values are expected to be few and distributed at random, in general, no replacement or imputation will be performed. Missing values will not be considered in the denominators for proportions. For many registries, if no information about a condition is given it indicates that the condition has not occurred, e.g. lack about a heart failure before the index date must be interpretation as that a heart failure has not happen.

The statistical analysis will be conducted using the SAS® software (version 9.3 or later) on Windows™ (SAS Institute, North Carolina, US) or using R statistical program (version 3.5.0 or later).

10.1 Primary Safety Endpoint(s)

10.1.1 Primary Analysis

All descriptive analyses outlined below will performed in the Nocdurna ® cohort, the LUTS group, and stratified by subgroups (elderly patients aged ≥65 years, patients with and without contraindications) as shown in Table 10. The study objectives are descriptive and no hypothesis have been formulated. Comparative analysis are done in secondary objective 7, as described in section 10.2.8.

10.1.2 Incidence of symptomatic hyponatraemia

The incidence rate of the primary outcome reported since index date in the study period will be modelled using a Poisson regression model and expressed as number of cases per 1000 patients-years at risk (+- 95% CI) for the Nocdurna ® group and the LUTS contextual cohort, separately. Person-period at risk is defined according to person-time observed from the index date to the first right censoring event. The dependent variable will be number of events for each person and the independent variable will be treatment, age class, and gender. Stratum-specific incidence rates will also be examined giving rates divided by gender, first month after index date and events occurring after the first month after the index date. Also incidence rates for patients with an age above or equal to 65 years will be calculated. If the model does not converge/modelling assumptions are not met, only unadjusted rates will be presented. This gives the following high level table shell.

Table 4. High level output description of the Poisson regression

	Nocdurna ®			LUTS		
	All patients	Male	Female	All patients	Male	Female
All events	X (x-x)	X (x-x)	X (x-x)	X (x-x)	X (x-x)	X (x-x)
First month	X (x-x)	X (x-x)	X (x-x)	X (x-x)	X (x-x)	X (x-x)
After first months	X (x-x)	X (x-x)	X (x-x)	X (x-x)	X (x-x)	X (x-x)
>= 65 y, All events	X (x-x)	X (x-x)	X (x-x)	X (x-x)	X (x-x)	X (x-x)

A complete table is shown in Table 9

A SAS macro for doing the above analysis has been developed and is described and attached in section 16.2 of this report. The analysis of events during the first month will limit the exposure time to a maximum of 30 days, while the analysis of events after the first month will subtract 30 days for the exposure time. However, there will also be patients that are enrolled late in the study e.g. in the month of December and these patients will have an exposure time of less than 30 days. It must be noted that the analysis of events after the first month is having an immortal time bias, but this bias is expected to be small, since (hopefully) very few patients will die or emigrate during the first month.

For both the Nocdurna ® and the LUTS group incidence rates (number of events/ 1000 person-years) will be estimated with 95% CIs, together with number of subjects in the group, number of events, the sum of the person years, the mean unadjusted rate of events (events/1000 person-years), the variance of unadjusted rate, number of patients with more than 1 event, the number of events in subjects with more than 1 event, the incidence rate (with 95 % CI), the standard error of mean of the incidence rate, and the scale. There is only one scale factor for each model.

The background for the study is to see how well physicians adhere to the labels contraindications, including history of hyponatremia. To investigate how the hazard of hyponatremia more precisely develops in time, hazard functions, based on Cox regression models for time to first event since index date (using the same analysis as in the Poisson model) will be plotted as a function of time. This figure should be generated for the primary objective, where 6 curves should show on the same figure, 2 curves for treatment and 3 curves for age class, 2*3 = 6 curves in total.

If recurrent events have been observed, a Cox model for recurrent events will be applied. Many recurrent events are in this context defined as more than 5% of the patients having more than 1 event. The approach for the analysis of the outcome will in that case follow the lines shown in the SAS documentation in example 87.10 using PROC PHREG with analysis of recurrent events (https://documentation.sas.com/?cdcId=pgmsascdc&cdcVersion=9.4_3.3&docsetId=statug&docsetTarget=statug_phreg_examples10.htm&locale=en). To be considered as recurrent events, diagnoses should be documented during 2 separate hospitalizations.

There will also be created a figure for the recurrent events where the time period between the first and the following events can be identified **Figure 31**. The time period between two events to be calculated as two separate events are 30 days based on experience from clinical studies for stabilising the sodium levels in the blood (PPD personal comm.).

The Nocdurna ® population will be divided into two groups, one group following the intended usage of the drug as described in the SmPC, the other group not following the intended usage, e.g. patients with a heart failure before starting the drug usage. The analysis of the primary objective will be repeated for these two groups, excluding the LUTS patients in this analysis.

10.1.3 Sensitivity Analyses

Sensitivity analyses will be performed to assess the robustness of the study findings:

The assumptions underlying the construction of Nocdurna ® treatment episodes will be tested. The length of the permissible gap will be shortened. For overlaps of two subsequent prescriptions, beginning of the second prescription will be shifted to the end of the first reducing the permissible gap to zero days. Table shells for this sensitivity analysis are shown from Table 45 to Table 51. The estimation of prescription duration will also be examined. Instead of estimating prescription duration based on the recommended daily dose of Nocdurna ® (1 oral lyophilisate), the dose actually prescribed to the individual patient will be considered (Sweden, Denmark). This analysis will be subject to availability of data on individual dosage instructions in the database/registry. The

method for this analysis will be the following. All dosing texts will be listed in a frequency table sorted with the most frequent text at the top. This table will be moved to EXCEL and a manual coding of the 98% of the most frequent dosing text will be done. The information will be moved back into SAS and the numeric value of the dosing instruction will be used in the sensitivity analysis as described above. Only the Nocdurna ® patients will have their dosing changed in this way. If the dosing text is informing the patient to use the drug 'as needed/vid behov/as explained or similar' this will be interpreted as 0.5 tablets per day. Often will the dosing text be like this without a specific instruction to the user. Table shells for this sensitivity analysis are shown from Table 52 to Table 58. This analysis is only possible in Sweden where the prescribing text is available.

The first sensitivity with shortened gap is expected to give a lower number of events, and at the same time also reduce the exposure time so the effect on the incidence rate cannot be predicted.

10.2 Secondary Safety Analyses

10.2.1 Secondary objective 1: Demographic and health characteristics

Demographic characteristics will be presented for both the Nocdurna ® and LUTS cohorts based on the index date. Other co-existing risk factors for primary and secondary outcomes of interest is also summarised. Characteristics will be described overall by cohort and stratified by sub-populations (elderly patients aged ≥65 years, patients with and without contraindications, patients with heart failure as used in section 10.2.7). The table shell is shown in Table 10 and will be repeated for the above sub-populations.

10.2.2 Secondary objective 2: Incidence of hyponatraemia requiring hospital intensive care

The analysis of hyponatraemia requiring hospital intensive care will be performed analogously to the analysis of incident events of symptomatic hyponatraemia (see 10.1.2). This analysis can only be done for Swedish data using the National Intensive Care Register from Värmland covering more than 90% of the Swedish intensive care units. ICU care for other reasons than hyponatraemia will not the included, while both primary and secondary diagnose codes for hyponatraemia will be counted.

10.2.3 Secondary objective 3: Incidence of clinically significant hyponatraemia

Analyses of incident and recurrent events of clinically significant hyponatraemia (<130 mmol/L) will be performed analogously to symptomatic hyponatraemia (see 10.1.2). Analyses will be performed among patients residing in the regions covered by the Danish National Laboratory Database Research Table. There will be 4 analysis stratified by the actual level of sodium concentrations where a *mild* hyponatraemia is a serum sodium concentration above 130 to less than 135 mmol/L, *moderate* is a serum sodium concentration of above 125 to less than 130 mmol/L, and *severe* is a serum sodium concentration of less than or equal to 125 mmol/L and the above specified as clinically significant hyponatraemia (<130 mmol/L)

The potential lack of serum sodium measurements, differences in the likelihood of being tested and intensity of testing will be addressed by describing the distribution of risk factors and background characteristics (e.g., relevant demographic and other risk factors such as comorbidities and co-medication) for tested and non-tested patients. The table shell for this analysis is shown in Table 12 and is repeating the baseline table, but only for the patients from 4 out of 5 Danish regions.

10.2.4 Secondary objective 4: All-cause mortality

The analysis of all-cause mortality will be performed analogously to that of incident events of symptomatic hyponatraemia, from the index date (see 10.1.2). Using a Poisson regression for mortality instead of a classical survival analysis make it possible to direct compare mortality with the other events rates in the study.

10.2.5 Secondary objective 5a: Incidence of major cardiovascular events

The analysis of incident MACE will be performed analogously to that of incident events of symptomatic hyponatraemia (see 10.1.2), from index date. Fatal and non-fatal MACE and VTE events will be assessed separately and this is possible in Denmark and Sweden.

In addition, time to events requiring hospital intensive care and cardiovascular death, respectively, will be described for patients with an incident diagnosis of MACE in the study time period. Events requiring hospital intensive care will be defined as a primary or secondary diagnosis of MACE recorded in a hospital intensive care unit (reported in Sweden only). Cardiovascular death is defined as a relevant diagnosis recorded as the underlying or contributing cause of death (reported for Sweden and Denmark). The description will be the analysis with number of subjects, mean (SD), median, range, interquartile range, and missing values as shown in Table 21 and Table 22 in Sweden and Denmark, respectively.

10.2.6 Secondary objective 5b: Incidence of major venous thromboembolic events

The analysis of incident VTE events will be performed analogously to that of incident events of symptomatic hyponatraemia (see 10.1.2), from index date.

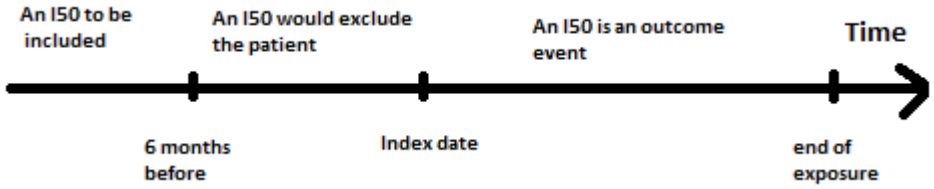
Similar to MACE, time to events requiring hospital intensive care and death from a VTE event, respectively, will be described for patients with an incident diagnosis of VTE in the study time period. The description will be the analysis with number of subjects, mean (SD), median, range, interquartile range and missing values as shown in Table 25 and in Table 26 in Sweden and Denmark, respectively.

10.2.7 Secondary objective 6: Incidence of acute exacerbation of congestive heart failure

A new population will need to be established for this outcome, a population of patients with prevalent chronic heart failure (still divided in Nocdurna ® and LUTS). Prevalent chronic heart failure will be defined as ever having had a primary or secondary diagnosis of heart failure (ICD-10: I50) before the index date, but no recorded primary diagnosis of heart failure from hospital inpatient care or the acute and emergency ward in the 6 months prior to the index date (6 months

are programmed as 180 days). Among these patients, acute exacerbation of heart failure will be defined as a primary diagnosis of acute or acute-on chronic heart failure from hospital inpatient care or the acute and emergency ward, or death from heart failure as the underlying or contributory cause. It is obvious that this population will be much smaller than the original population. A new baseline table will also need to be established for these patients, as specified in Table 28.

Figure 2. Inclusion, exclusion time periods and events for secondary objective 6.



The analysis itself of acute exacerbation of congestive heart failure will be performed analogously to that of incident events of symptomatic hyponatraemia (see 10.1.2).

10.2.8 Secondary objective 7: Comparative analyses

Where possible, for the comparative analyses of primary and secondary outcomes of interest, the same analyses (Poisson regression) as in Section 10.1.2 will be applied but now with treatment group (Nocdurna ®/LUTS) as an additional factor. Patients in the two groups will have their exposure time terminated when patients switch treatment (from Nocdurna to LUTS treatment or from LUTS treatment to Nocdurna). To investigate if the incidence rate ratio (IRR) for the Poisson regression of Nocdurna ® to LUTS depend on confounders, treatment by confounder interaction terms will be investigated to see if and to what extent the IRR depend on the respective confounding factor (age class and gender). A SAS macro have been developed for performing the analysis and is documented in 16.2. The output of the analysis is shown in Table 29. The analysis will show the percent change in the Nocdurna ® group as compared with the LUTS group (using the other variables as covariates), the percent change in the age class 65 to<=75 year and above or equal 75 years as compared with the <65 year age class, and the percent change in the males as compared with the females. Also the 95% CI and the standard error of the means change are calculated, together with the p-value. The scale value for the model is calculated. The LUTS group is used as reference to ease the interpretation. Observe also that the Poisson regression is the same as the Section 10.1.2, but the output is changed to find the incidence rate ratios (IRR) instead of the incidence rates (IR) themselves. If the model does not converge/modelling assumptions are not met, only unadjusted rate ratios will be presented.

10.2.9 Secondary objective 8: Cardiovascular and thromboembolic events of interest resulting in treatment withdrawal

The analysis of this outcome will be performed analogous to that of incident events of symptomatic hyponatraemia in Section 10.1.2, but only for the Nocdurna ® patients. MACE and VTE events considered to be associated with treatment cessation will be those events for which the event date occurs within 14 days prior to the treatment cessation date. Serious MACE and VTE events will be defined as a primary or secondary diagnosis of MACE or VTE recorded in a hospital intensive care unit. This differs from the normal definition of serious adverse event. This can only be evaluated in Sweden.

The analysis will first calculate the treatment cessation date and then within a 14 days window before the treatment cessation date examine if there is a MACE or VTE event reported from the intensive care register.

Secondary objective 9: Incidence rate in patients stratified according to the label by proxy

The analysis of this outcome will be performed analogous to that of incident events of symptomatic hyponatraemia but only for the Nocdurna ® patients. The subgroup of patients adhering to the label will be defined by a proxy based on diagnosis and contra-indications as stated in the SmPC and the data for classifying the patients according to contraindications should be done as available in the respective registries.

Two population will be created for all Nocdurna ® patients, one with contra-indication for treatment and another as the remaining Nocdurna ® patients without contra-indication. The contra-indication for treatment must be present before the first recorded dispensation of Nocdurna ®.

The following diseases will be considered as contraindications for the prescription of Nocdurna ®, if the diseases are found before or at the index date.

- History of hyponatraemia
- Polydipsia
- Congestive heart failure (chronic)
- Kidney disease (chronic kidney disease stage 3 and over)
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

The ICD 10 codes for the above can be found in the given in Table 71. The analysis will be done by using the SAS macro ‘Nocdurna_mac’ and changing the macro call with ‘compare=Off label’ and creating a class group with ‘Off label’ instead of ‘LUTS’ as described in section 16.1

The analysis of the sub-population will be done for the primary objective and for secondary objective 2, 3, 4, 5a, 5b and 6.

Observe that this analysis is changed from the description in the study protocol.

10.3 Data used for meta-analysis

The protocol specifies that a meta-analysis should be included in the final report planned for December 2023. However, it is important to already now to investigate similarities and differences in the databases to be able to suggest the correct analysis to be done and not comparing different data from the three countries. The statistical methods will also by specified in this SAP. The calculations will be made by the Swedish statistician, e.g. no calculations are needed by BIPS or Statistics Denmark as shown in Table 6.

Table 5. Similarities and differences between the outcome measures in the 3 countries

Objective	Denmark	Germany	Sweden	Meta-analysis
Primary objective, rate of low Na by diagnose code	Recorded from hospitals	Recorded from practitioners and specialists and hospitals*)	Recorded from hospitals	Maybe
Sec. Objective 1, descriptive statistics	Data	Data	Data	OK
Sec. Objective 2, low Na treated at ICU	No data	No Data	Data from a specialized ICU register	Not possible
Sec. Objective 3, low lab. values of Na	Clinical database	No Data	No Data	Not possible
Sec. Objective 4, All-cause mortality	Data	Data (no reason for death)	Data	OK
Sec. Objective 5a, MACE	Recorded from hospitals	Recorded from practitioners and specialists and hospitals*)	Recorded from hospitals	Maybe
Sec. Objective 5b, VTE	Recorded from hospitals	Recorded from practitioners and specialists and hospitals*)	Recorded from hospitals	Maybe
Sec. Objective 6, CHF	Recorded from hospitals	Recorded from practitioners and specialists and hospitals*)	Recorded from hospitals	Maybe
Sec. Objective 7, Comparing	Repeat primary analysis + sec. 2, 3, 4, 5a, 5b, 6.	Repeat primary analysis + sec. 2, 3, 4, 5a, 5b, 6.	Repeat primary analysis + sec. 2, 3, 4, 5a, 5b, 6.	Look at the other rows

Nocdurna ® vs LUTS				
Sec. Objective 8, treatment withdrawal	No Data	No Data	Data from drug registry	Not possible
Sec. Objective 9, treatment on label	Repeat primary analysis + sec. 3, 4, 5a, 5b, 6.	Repeat primary analysis + sec. 4, 5a, 5b, 6.	Repeat primary analysis + sec. 2, 4, 5a, 5b, 6.	Primary obj. + secondary 1-6

Abbreviations: ICU = Intensitive Care Unit, MACE = major cardiovascular events, VTE = major venous thromboembolic events, CHF = congestive heart failure. *) German data could be sub-divided and German data are discharge data (in-patient hospital care).

Comment to the table about meta-analysis.

It is obvious that there are major differences between the data collections in Germany on one side and Denmark/Sweden on the other side and also some difference between Denmark and Sweden. The Germany database also contains information from primary care and specialists, while the registries in Denmark/Sweden only contains information from hospitals, both in- and out-patient care. This issue concerns the primary objective, and secondary objective 5a, 5b, 6, 7 and 8. The effect will make the rates of the events higher in Germany, since events in primary care also are counted. However, the difference in effect between Nocdurna ® and LUTS could be expected to be more similar than the rate of events since there should be a similar increase in both groups when counting events in primary care. Also Danish and Swedish registries contain cause of death information (ICD 10 codes) that could partly be covered by German registries if the patient is hospitalized before dying at the hospital. Nocdurna ®

The deterministically linkage used by BIPS might also give a larger variance than the person-id linked data from Denmark and Sweden. However, the effect difference should be the same.

In secondary objective 2, 3, and 8 the data is only coming from one country and a meta-analysis is not possible, while secondary objective 9 is repeating the previous analysis taking contraindications for Nocdurna ® into consideration.

10.4 Meta-analysis of incidence rates

The descriptive tables in secondary outcome 1 will for the numeric variables like age be recalculated to give overall number of patients, mean and standard deviation, while the categorical variables will be recalculated to give frequencies and percentage covering the total population in Denmark, Germany, and Sweden. The method for re-calculation is shown in Figure 3.

The incidence rates (not the incidence rates ratios between the outcomes) will be combined by calculating the weighted mean and a new standard deviation for the 95% CI around the combined mean. The new standard deviation will be calculated according to the formulae given below.

Figure 3. Formulae for combining groups.

	Group 1 (e.g. males)	Group 2 (e.g. females)	Combined groups
Sample size	N_1	N_2	$N_1 + N_2$
Mean	M_1	M_2	$\frac{N_1M_1 + N_2M_2}{N_1 + N_2}$
SD	SD_1	SD_2	$\sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1M_2)}{N_1 + N_2 - 1}}$

From (Cochrane Handbook, 2011)

10.5 Meta-analysis of incidence rate ratios

The results for incidence rate ratios (calculated according to secondary objective 7) will undergo a meta-analysis and be combined between the countries according to this section and illustrated in the tables (Table 61 to Table 65) and the figures (Figure 21 to Figure 30) . The outcomes included in the meta-analysis are the primary objective, and for the secondary objectives 4, 5a, 5b, and 6.

The approach used is published by (Senn et al., 2011)

First the heterogeneity will be calculated and a p-value for the test if there is any heterogeneity will be calculated.

The formula used is computes I-square for the Q test for odds ratios as

$I^2 = \max(100\% \times (Q - (k - 1))/Q; 0)$

Where k is the number of strata and Q is a Q test for homogeneity of odds. This is implemented in the PROC FREQ procedure in SAS.

For interpreting I^2, (Higgins et al., 2003) suggest

I^2 = 0 %, no heterogeneity,
I^2 = 25 %, low heterogeneity,
I^2 = 50 %, moderate heterogeneity,
I^2 = 75 %, high heterogeneity.
We should expect low heterogeneity.

A plot similar to the forest plot will be created for each of the outcomes showing the overall rate as illustrated in figure Figure 21. A Galbraith plot gives the same information as the forest plot, but

with another focus, where countries deviating from the mean are more easily detected as seen in Figure 21.

A funnel plot will be made. In a funnel plot should all points be in a triangle around the center vertical line as in Figure 22. If the parts of the triangle is missing, there could be a bias in the distribution or a classical bias in not publishing studies with negative results.

The sensitivity plot, in Figure 22, show the difference between a fixed model and a random model. The y-value for low values on the horizontal axis gives the value of a fixed model. In this figure the bold curve is decreasing indicating that the random effect is lower in absolute difference between treatments than the fixed effect model. It should be expected that a random model will have larger confidence intervals.

An analysis of using a fixed effect or random effect model demands to have heterogeneity analyzed before judgements can be done and even with these analyses a precise determination can be difficult to make. If we are measuring the same effect a fixed effect model should be used. Otherwise, a random effect model should be used. If we were joining different studies from different countries with different outcome, we should use a random effect model. In this case we are measuring the same outcome, but in different countries and in different administrative systems and each country will have several administrative systems for the health care. Both random and fixed effect models analysis will be planned. An outcome table for the combined effect using both fixed effect models will be created showing the model type, the method, the estimated combined difference in treatment, the standard of the estimated combined difference together with upper and lower 95% CI of the estimated combined difference. An example is shown in Table 61.

10.6 Supportive Secondary Endpoints

N/A

10.7 Explorative /Tertiary Effectiveness Endpoint(s)

N/A

11 INTERIM ANALYSES

In addition to the final study report planned for December 2023, there will be two annual interim reports (one per year) on study progress and any emerging safety data. These are planned for December 2021 and December 2022. Both country-specific and pooled results (meta-analysis) will be presented in the final report, where data are available.

There will not be any adjustment for multiple comparisons doing several analyses, nor corrections where multiple comparisons are done.

12 RISK-BENEFIT ASSESSMENT

N/A

13 CHANGES FROM THE PROTOCOL

The statistical analysis are described in further details and explanatory figures have been added, compared with the outlines in the protocol.

The protocol states that 'Fatal and non-fatal MACE and VTE events will be assessed separately', but this is only possible in Denmark and Sweden. The SAP is updated.

The protocol stated that 'The length of the permissible gap will be varied (shortened or lengthened).', while the SAP specified 'The length of the permissible gap will be shortened'. Also the following has been added '. If two treatments with different ATC-codes are dispensed (or prescribed) on the same day only the treatment with the highest number of supplied days should be kept in the analysis.', since the previous formulation would give too long treatment periods.

Protocol stated in section 9.3.21 that 'If, recurrent events have been observed, a Cox model for recurrent events may be applied which will be detailed in the SAP.' The SAP specifies that this analysis will be presented if more than 5% of the patients has recurrent events.

Meta-analysis is in the protocol 'specified as random effect model', but the analysis has been expanded to both random and fixed effect model in the SAP and this is also reflected in the table shells.

Protocol stated that 'All adverse events/reactions collected for the study will be recorded and summarized in the interim *safety* analysis and in the final study report.' The SAP specifies that 'All adverse events/reactions collected for the study will be recorded and summarized in the interim analysis and in the final study report'. The word 'safety' was deleted since all statistical analysis will be presented in the yearly reports, except the meta-analysis.

The analysis of contraindications have been simplified and corrected compared with the protocol. Only one subpopulation for defining contraindications will be created, not the suggested 3 sub-population, so that the extra medical conditions in secondary objective 5a, 5b, and 6 have been omitted, since it is not reasonable to have different contraindication at baseline for a possible future event. The usage of concomitant medical usage has also been omitted, since it is the condition at baseline that must determinate initiation of Nocdurna ® usage, not a future concomitant medical prescription, unknown to the prescribing physician at the index date.

14 TABLES, LISTINGS AND FIGURES

LIST of TABLES

LIST of FIGURES

An overview of the different tables divided by country of origin and objective is given below.

Observe that Table 1 to Table 7 are used in the ordinary text in this Statistical Analysis Plan.

Table 6. Overview of the different tables by country and objective.

Objective	Denmark	Germany	Sweden
Primary obj.	Table 9	Table 9	Table 9
Sec obj. 1, descriptive	Table 8, Table 10, Table 11, Table 12	Table 8, Table 10, Table 11	Table 8,Table 10, Table 11
Sec obj. 2, ICU	N/A	N/A	Table 13
Sec obj. 3; lab Na	Table 14, Table 15, Table 16, Table 17	N/A	N/A
Sec obj. 4, mortality	Table 18	Table 18	Table 18
Sec obj. 5a, MACE	Table 19, Table 20, Table 22	Table 19	Table 19, Table 20, Table 21,
Sec obj. 5b, VTE	Table 23, Table 24, Table 26	Table 23	Table 23, Table 24, Table 25
Sec obj. 6, CHF	Table 27	Table 27	Table 27
Sec obj. 7, comparative	Table 29, Table 30, Table 31, Table 32, Table 33, Table 34, Table 35, Table 36	Table 29, Table 30, Table 31, Table 32, Table 33, Table 34, Table 35, Table 36	Table 29, Table 30, Table 31, Table 32, Table 33, Table 34, Table 35, Table 36
Sec obj. 8, treatment withdrawal	N/A	N/A	Table 37
Sec obj. 9, contraindications	Table 38, Table 40, Table 41, Table 42, Table 43, Table 44	Table 38, Table 41, Table 42, Table 43, Table 44	Table 38, Table 39, Table 41, Table 42, Table 43, Table 44
Sensitivity, reduced gap	Table 45, Table 47, Table 48, Table 49, Table 50 Table 51	Table 45, Table 48, Table 49, Table 50 Table 51	Table 45, Table 46, Table 48, Table 49, Table 50 Table 51

Sensitivity, using prescribed dose	Table 52, Table 54, Table 55, Table 56, Table 57, Table 58	N/A	Table 52, Table 53, Table 55, Table 56, Table 57, Table 58
Meta-analysis			Table 59, Table 60, Table 61, Table 62, Table 63, Table 64, Table 65
Optional, Table 66			

Observe that Table 67 to Table 73 are to be used for giving instructions for the SAS programming.

An overview of the different figures divided by country of origin is given below. Figure 1 to Figure 3 is used in the text.

Table 7. Overview of the different figures by country and objective.

Objective	Denmark	Germany	Sweden
Primary obj.			
	Figure 6	Figure 6	Figure 6
Sec obj. 1, descriptive, age and exposure time	Figure 7, Figure 8, Figure 9, Figure 10, Figure 11, Figure 12, Figure 13, Figure 14	Figure 7, Figure 8, Figure 9, Figure 10, Figure 11, Figure 12, Figure 13, Figure 14	Figure 7, Figure 8, Figure 9, Figure 10, Figure 11, Figure 12, Figure 13, Figure 14
Sec obj. 2, ICU	N/A	N/A	Figure 15
Sec obj. 3; lab Na	Figure 16	N/A	N/A
Sec obj. 4, mortality	Figure 17	Figure 17	Figure 17
Sec obj. 5a, MACE	Figure 18	Figure 18	Figure 18
Sec obj. 5b, VTE	Figure 19	Figure 19	Figure 19
Sec obj. 6, CHF	Figure 20	Figure 20	Figure 20
Sec obj. 7, comparative	N/A	N/A	N/A
Sec obj. 8, treatment withdrawal	N/A	N/A	N/A

Sec obj. 9, contraindications	N/A	N/A	N/A
Sensitivity, reduced gap	N/A	N/A	N/A
Sensitivity, using prescribed dose	N/A	N/A	N/A
Meta-analysis			Figure 21 to Figure 30
Optional, Figure 31			

Footnote: The following figures are an option for BIPS Figure 7, Figure 8, Figure 9, Figure 10, Figure 11, Figure 12, Figure 13, Figure 14

The following are the table shells.

Table 8. Patient disposition with number of patients in *country.*

	All Nocdurna ® patients	**Nocdurna ®, Male**	**Nocdurna ®, Female**	**All LUTS patients**	**LUTS, Male**	**LUTS, Female**
Number of extracted patients	Xx	Xx	Xx	Xx	Xx	Xx
Number of patients above 18 yy	Xx	Xx	Xx	Xx	Xx	Xx
Number of patients with 1 drug dispensation*)	Xx	Xx	Xx	xx	xx	xx
Excluded, age/gender is missing						
Excluded, vasopressin treated	Xx	Xx	Xx	Xx	Xx	Xx
Excluded, <12 month records before index date	Xx	Xx	Xx	Xx	Xx	Xx
LUTS drugs before study period start	N/A	N/A	N/A	Xx	Xx	Xx
Sum Excluded	Xx	Xx	Xx	Xx	Xx	Xx
Number of patients in the HF cohort, secondary objective 6.	Xx	Xx	Xx	Xx	Xx	Xx

*). Exclusion of patients with multiple desmopressin drugs dispensed on the index date. SOURCE DOCUMENT: SUMTAB.SAS GENERATED: 22:53:48 16JAN2021 DB version DEV: Simulated data, USERID: LAJ

Figure 4. Cohort selection flowchart for exploratory analysis, optional figure.

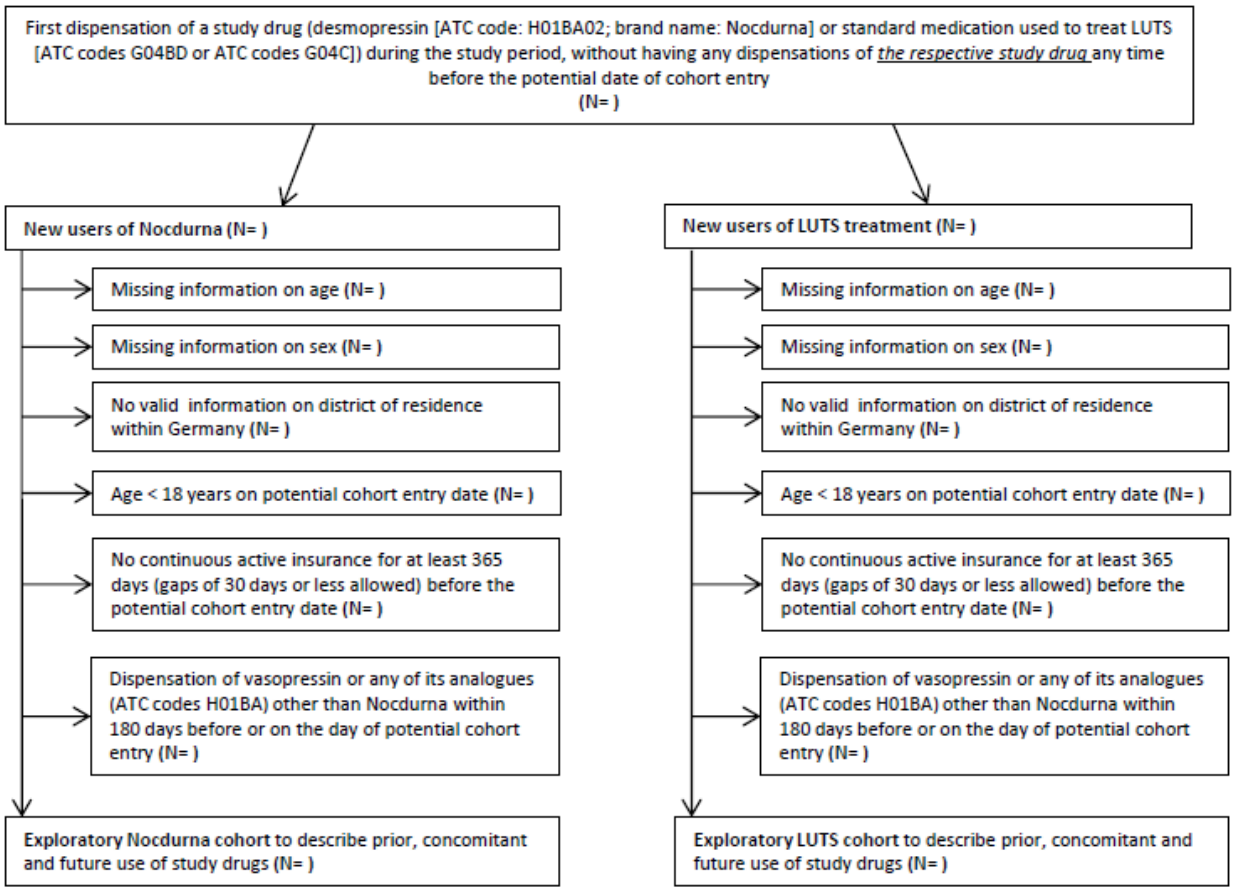


Figure 5. Cohort selection flowchart for main analysis, optional figure.

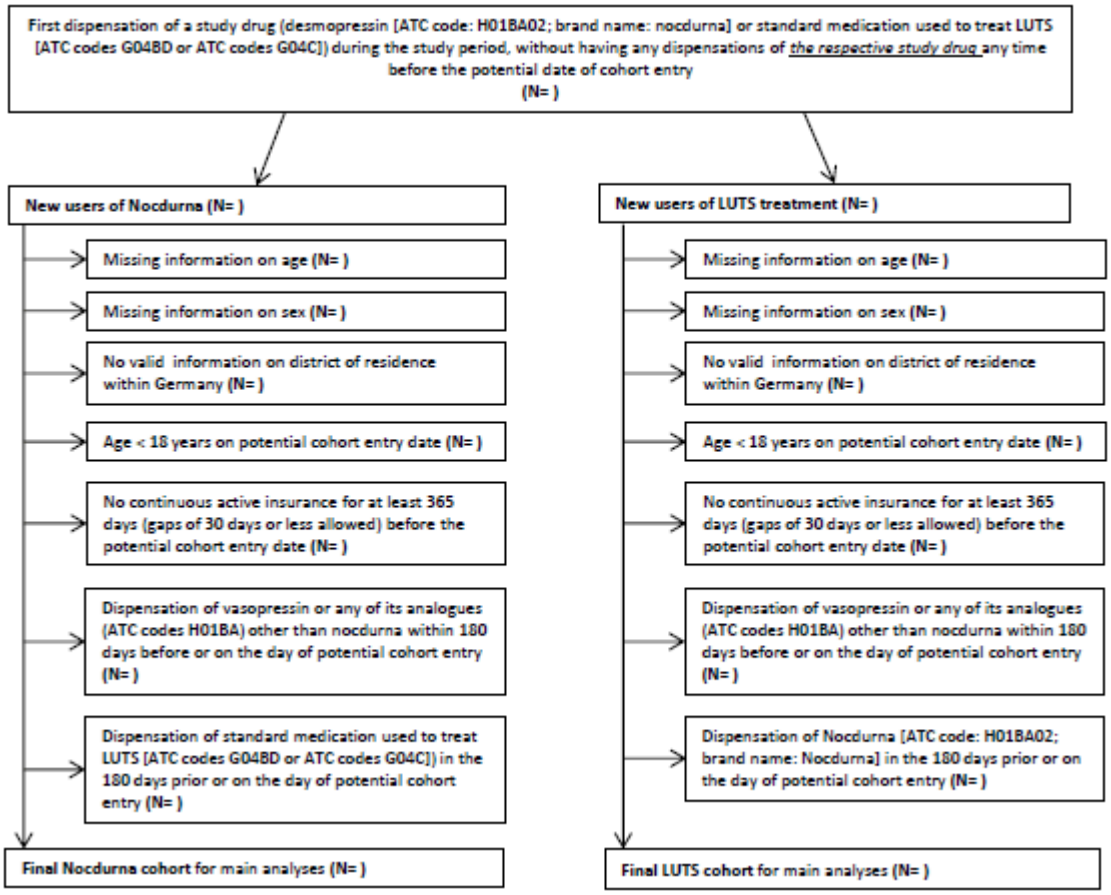


Table 9. Primary objective. Incidence of symptomatic hyponatraemia in *country*.

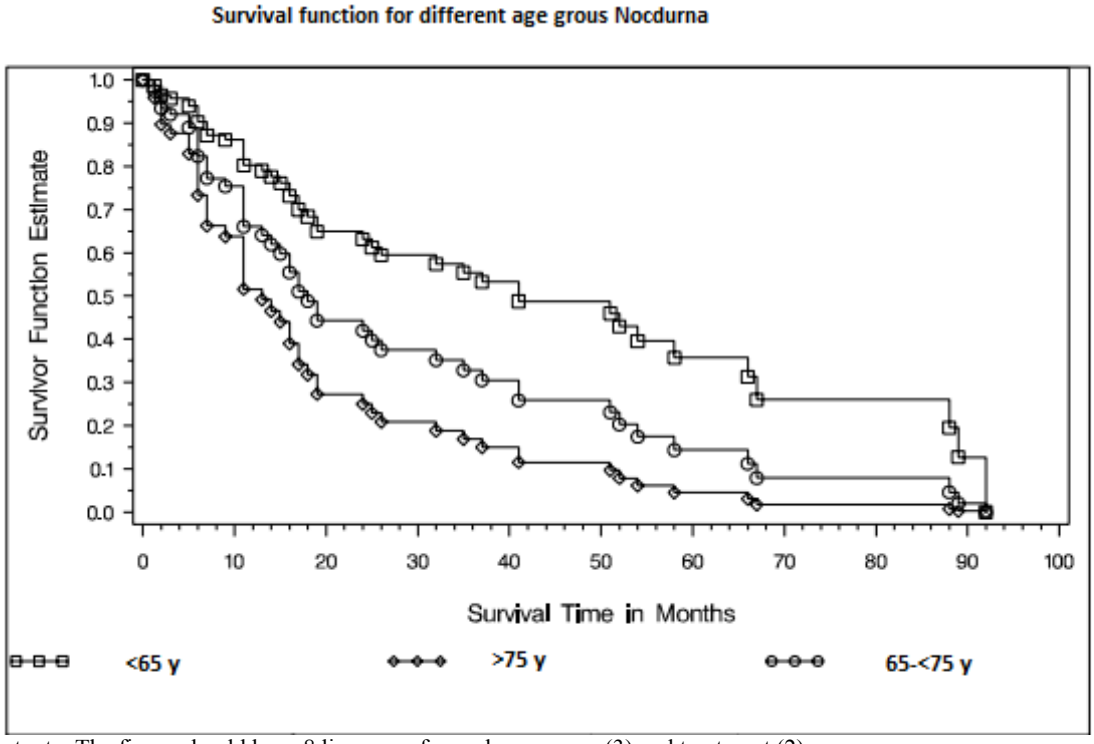
	All Nocdurna ® patients	Nocdurna ®, Male	Nocdurna ®, Female	All LUTS patients	LUTS, Male	LUTS, Female
Variable, time period and population						
All patients - All exposure time						
Number of subjects	3512	2289	1223	1488	931	557
Number of events	493	367	126	129	93	36
Total person years (y)	510.4	335.7	174.7	219.5	138.4	81.0
Mean unadjusted rate of events (events/1000 person-years)	1201.8	1364.8	896.9	759.7	866.9	580.5
Number of patients with more than 1 event	29	25	4	8	5	3
Number of events in patients with more than 1 event	60	52	8	16	10	6
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx

Incidence rate (95 % CI)	861.40 (798.94 - 928.74)	1073.58 (989.55 - 1164.75)	688.70 (608.23 - 779.81)	532.61 (466.19 - 608.49)	662.92 (565.25 - 777.46)	427.68 (341.35 - 535.85)
Standard Error of Mean	33.08	44.64	43.66	36.19	53.91	49.20
Scale - one value for each model	0.7468	0.7796	0.6830			
Events first month after Index date						
Number of subjects	3512	2289	1223	1488	931	557
Number of events	129	98	31	28	18	10
Total person years (y)	491.4	321.7	169.6	214.7	134.5	80.2
Mean unadjusted rate of events (events/1000 person-years)	312.8	362.0	220.8	161.9	176.6	137.3
Variance of unadjusted rate	642.4	645.5	636.7	661.6	683.9	625.5
Number of patients with more than 1 event	.	.	.	1	1	.
Number of events in patients with more than 1 event	.	.	.	2	2	.
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx
Incidence rate (95 % CI)	221.51 (201.40 - 243.62)	285.44 (257.50 - 316.41)	163.73 (139.55 - 192.11)	112.50 (94.11 - 134.48)	126.37 (100.58 - 158.78)	114.02 (87.49 - 148.60)
Standard Error of Mean	10.75	15.00	13.35	10.24	14.72	15.41
Scale - one value for each model	0.4641	0.4882	0.4168			
Events after first month and onwards						
Number of subjects	2324	1536	788	1017	639	378
Number of events	229	169	60	58	44	14
Total person years (y)	406.1	268.8	137.3	179.2	113.6	65.6
Mean unadjusted rate of events (events/1000 person-years)	650.5	720.6	513.7	366.3	415.8	282.7
Variance of unadjusted rate	611.2	610.4	613.6	603.0	619.4	575.3
Number of patients with more than 1 event	13	11	2	4	3	1
Number of events in patients with more than 1 event	26	22	4	8	6	2
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx
Incidence rate (95 % CI)	513.14 (465.63 - 565.51)	628.77 (565.80 - 698.74)	421.10 (359.52 - 493.23)	297.85 (249.79 - 355.15)	386.66 (314.79 - 474.93)	207.78 (151.08 - 285.75)
Standard Error of Mean	25.44	33.85	33.97	26.74	40.57	33.78
Scale - one value for each model	0.6639	0.6936	0.6043			
Patients >= 65 years						
Number of subjects	2435	1573	862	1038	650	388
Number of events	379	281	98	100	69	31
Total person years (y)	352.4	230.4	122.0	152.6	96.6	56.0

Mean unadjusted rate of events (events/1000 person-years)	1332	1519	993	843	915	722
Variance of unadjusted rate	648	646	649	646	661	620
Number of patients with more than 1 event	22	19	3	7	4	3
Number of events in patients with more than 1 event	46	40	6	14	8	6
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx
Incidence rate (95 % CI)	994.08 (912.02 - 1083.53)	1225.03 (1115.13 - 1345.76)	801.29 (695.41 - 923.29)	616.35 (527.97 - 719.52)	725.40 (600.62 - 876.09)	555.75 (432.23 - 714.58)
Standard Error of Mean	43.70	58.75	57.94	48.67	69.86	71.28
Scale - one value for each model	0.7701	0.7995	0.7140			

SOURCE DOCUMENT: TABLE1.SAS GENERATED: 22:53:48 16JAN2021 DB version DEV: Simulated data, USERID: LAJ

Figure 6. Primary objective. A Cox regression showing time to first event symptomatic hyponatraemia event stratified by patient group and age class in *country*.



Footnote: The figure should have 8 lines, one for each age group (3) and treatment (2).
SOURCE DOCUMENT: COX1.SAS GENERATED: 22:53:48 16JAN2021 DB version DEV: Simulated data, USERID: LAJ

Table 10. Secondary objective 1. Demographic and health characteristics in *country*.

	All Nocdurna ® patients	**Nocdurna ®, Male**	**Nocdurna ®, Female**	**All LUTS patients**	**LUTS, Male**	**LUTS, Female**
Age (year)						
N	230	100	230	100	230	100
Mean (SD)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)
Median	62.05	63.13	62.05	63.13	62.05	63.13
Range	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0
IQR	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0
Missing values	0	0	0	0	0	0
Repeat above 7 limes for						
Number of hospitalisations	…					
Number of emergency room visits	…					
Exposure time	…					

Gender, n and (%)						
Male	99 (43)	99 (43)	N/A	49 (49)	49 (49)	N/A
Female	131 (57)	N/A	131 (57)	51 (51)	N/A	51 (51)
Repeat the above 3 lines for						
Polyuria R35, please check national implementation of R35	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Polyuria R35.9A	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Nykturi R35.9B	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Pollakisuri R35.9C	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Diabetes mellitus; E10, E11, E12, E13 and E14	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Diabetes insipidus, E23.2	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Overactive bladder, N31.0, N31.2, N31.9, N39.4, R39.1 and ATC G04BD	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Benign prostatic hyperplasia, N40, D29.1 and ATC G04C	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Urinary tract infection, N39.0, N30, N10	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Polydipsia, R36.1	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Heart failure, I50	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Hypertension, I10	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Hyperlipidaemi, E78	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Atrial fibrillation, I48	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Obesity, E66	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Kidney disease, N18, N19	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Cystic fibrosis, E84	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Pre-eclampsia, O11, O14	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Chronic lung disease, J40-J47, J60-J70, J80, J82, J84, J95-J99	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Liver disease, K70-K77, F10 and ATC N07BB	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Cancer, C00-C43, C45-C97	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Prostate cancer, C61	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Bladder cancer, C67	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)

Dementia F00, F01, F02, F03, F04, G30, G31.0, G31.1	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Co-medication	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Loperamide, A07DA03	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Antidiabetics, A10	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Sulfonylureas including chlorpropamide, A10BB	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Amiodarone, C01BD01	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Antihypertensive, C02	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Diuretics, C03	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Special diuretics, C03A, C03B, C03C, C03D and C03E	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Beta blocking agents, C07	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Special beta blocking agents, C07B, C07C and C07D	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Calcium channel blockers and diuretics, C08G	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
ACE inhibitors, C09A	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Special ACE inhibitors, C09BA	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Angiotensin II receptor blockers, C09C	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Angiotensin II receptor blockers (combinations), C09D	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Lipid-modifying agents, C10	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Vasopressin and analogues (incl. desmopressin), H01BA	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Systemic corticosteroids, H02	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Antiepileptic, N03A	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Carbamazepine and lamotrigine, N03AF01 and N03AX09	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Non-selective monoamine reuptake inhibitors, N06AA	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Selective serotonin reuptake inhibitors, N06AB	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)

Chlorpromazine, N05AA01	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
NSAIDs, M01A	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Opioids, N02A	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Phenothiazines with aliphatic side-chain, N05AA	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Chlorpromazine, N05AA01	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Lithium, N05AN01	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Antidepressants, N06A	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Anti-inflammatory agents, non-steroids , M01A	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Overactive bladder, G04BD	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Benign prostatic hyperplasia, G04C	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Desmopressin, H01BA02	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Patients >= 65 years	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Repeat all the above rows for this population	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)

SOURCE DOCUMENT: DEMOGRAPHY_SWEDEN.SAS GENERATED: 22:53:48 16SEP2013 DB version DEV: ART_03, USER_ID LAJ.
Calculated on the index date, except for exposure time as defined in this SAP.

Table 11. Secondary objective 1. Demographic and health characteristics in *country* divided according to contraindications.

	Nocdurna ® patients					
	Without contraindications			With contraindications		
	Both gender	**Male**	**Female**	**Both gender**	**Male**	**Female**
Age (year)						
N	230	100	230	100	230	100
Mean (SD)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)
Median	62.05	63.13	62.05	63.13	62.05	63.13
Range	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0
IQR	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0
Missing values	0	0	0	0	0	0
Repeat the structure from the previous table (a long table!)						

SOURCE DOCUMENT: DEMOcontra_SWEDEN.SAS GENERATED: 22:53:48 16FEB2021 DB version DEV: ART_03, USER_ID LAJ.
Calculated on the index date, except for exposure time as defined in this SAP. Only patients from 4 out of 5 Danish regions reporting to the National Lab database.

Table 12. Secondary objective 1. Demographic and health characteristics in *Denmark* stratified according to patients with sodium measurements and patients without sodium measurements.

Repeat table shell from Table 10 and stratify according to patient with and without measurements.

Figures of continuous variables.

Figure 7. Secondary objective 1. A Boxplot of age divided by treatment group in *country*.

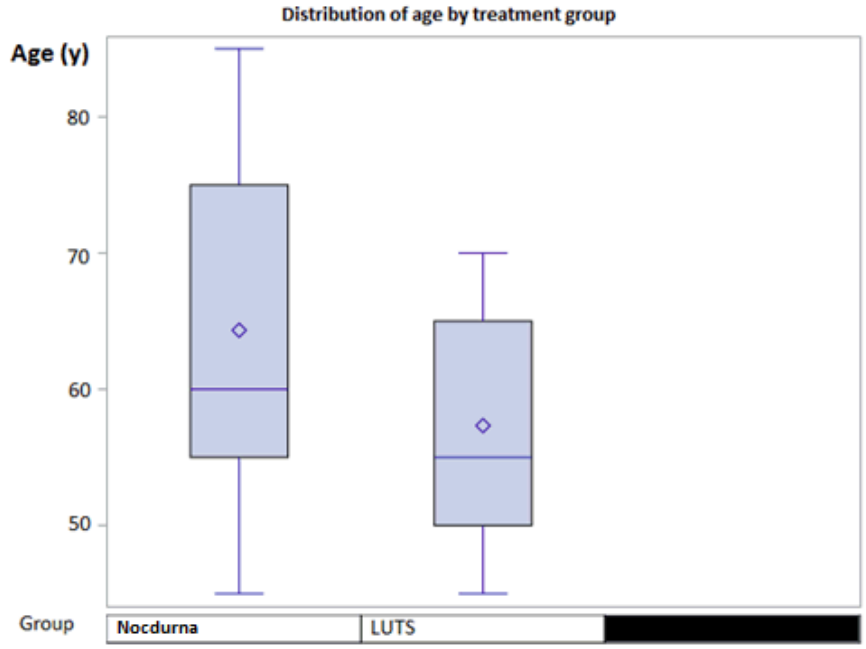


Figure 8. Secondary objective 1. A symmetry plot of age divided by treatment group in country (only one group is shown).

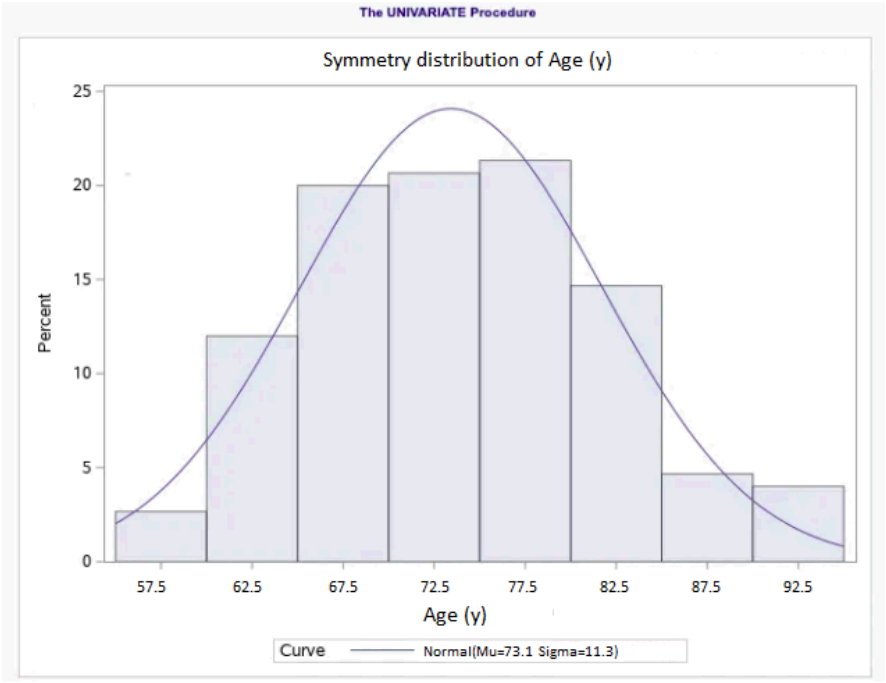


Figure 9. Secondary objective 1. A normal quantile plots of age divided by treatment group (Nocdurna ® and LUTS) in *country* (only one group is shown).

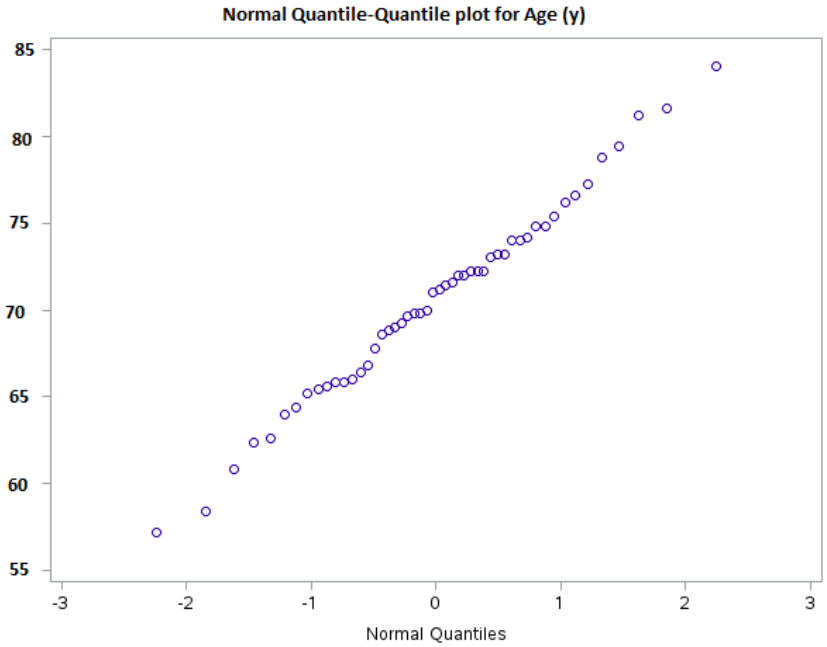


Figure 10. Secondary objective 1. A normal probability plots of age divided by treatment group in *country* (only one group is shown).

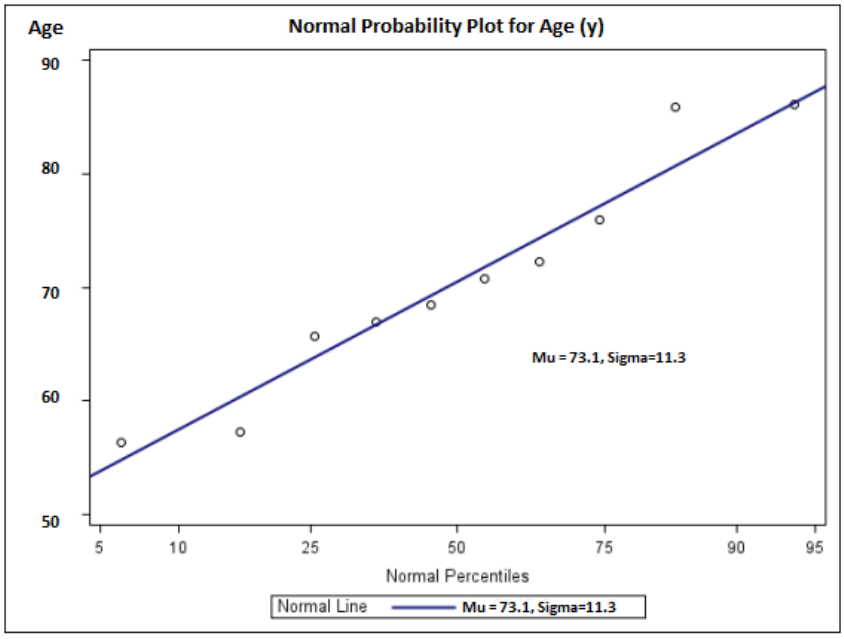


Figure 11. Secondary objective 1. A Boxplot of exposure time divided by treatment group in *country*.

Repeat Figure 7 with exposure time instead of age.

Figure 12. Secondary objective 1. A symmetry plot of exposure time divided by treatment group in country.

Repeat Figure **8** with exposure time instead of age.

Figure 13. Secondary objective 1. A normal quantile plots of exposure time divided by treatment group (Nocdurna ® and LUTS) in *country*.

Repeat Figure 9 with exposure time instead of age.

Figure 14. Secondary objective 1. A normal probability plots of exposure time divided by treatment group in *country*.

Repeat Figure 10 with exposure time instead of age.

Table 13. Secondary objective 2. Incidence of hyponatraemia requiring hospital intensive care (ICU) in *Sweden*.

Repeat Table 9 with changed outcome

Figure 15. Secondary objective 2. A Cox regression showing time to first event hyponatraemia requiring hospital intensive care (ICU) stratified by patient group and age class in Sweden.

Table 14. Secondary objective 3. Incidence of clinically significant hyponatraemia (lab value) in *Denmark*: serum sodium concentration <130 mmol/L

Repeat Table 9 with changed outcome

Table 15. Secondary objective 3. Incidence of hyponatraemia (lab value) in *Denmark* with mild hyponatraemia: serum sodium concentration 130 to<135 mmol/L

Repeat Table 9 with changed outcome

Table 16. Secondary objective 3. Incidence of hyponatraemia (lab value) in *Denmark* moderate hyponatraemia: serum sodium concentration 125 to<130 mmol/L

Repeat Table 9 with changed outcome

Table 17. Secondary objective 3. Incidence of hyponatraemia (lab value) in *Denmark* severe hyponatraemia: serum sodium concentration <125 mmol/L.

Repeat Table 9 with changed outcome

Figure 16. Secondary objective 3. A Cox regression showing time to first clinically significant hyponatraemia (lab value) stratified by patient group and age class in Denmark.

Table 18. Secondary objective 4. All-cause mortality in *country*.

Repeat Table 9 with all-cause mortality as outcome

Figure 17. Secondary objective 4. A Cox regression showing all-cause mortality by patient group and age class in *country*.

Table 19. Secondary objective 5a. Incidence of major cardiovascular events in *country*.

Repeat Table 9 with major cardiovascular events as outcome.

Figure 18. Secondary objective 5a. A Cox regression showing time to first major cardiovascular events stratified by patient group and age class in *country*.

Table 20. Secondary objective 5a. Incidence of major cardiovascular events divided in fatal and non-fatal events in Denmark and Sweden.

Repeat Table 9 with changed outcome and with the double number of rows to account for the divided outcome (fatal and non-fatal).

Table 21. Secondary objective 5a. Descriptive statistics of time to hospital intensive care (ICU) for MACE and time to cardiovascular death in Sweden.

Time to hospital intensive care	**All Nocdurna ® patients**	**Nocdurna ®, Male**	**Nocdurna ®, Female**	**All LUTS patients**	**LUTS, Male**	**LUTS, Female**
Time to hospital intensive care (days)						
N	23	10	13	50	30	20
Mean (SD)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)
Median	62.05	63.13	62.05	63.13	62.05	63.13
Range	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0
Interquartile ranges	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0
Missing values	0	0	0	0	0	0
Time to cardiovascular death(days)						
N	10	7	3	30	20	10

Mean (SD)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)
Median	62.05	63.13	62.05	63.13	62.05	63.13
Range	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0
Interquartile ranges	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0
Missing values	0	0	0	0	0	0

SOURCE DOCUMENT: DEMOGRAPHY_HOSP1.SAS GENERATED: 22:53:48 16SEP2013 DB version DEV: ART_03, USER_ID LAJ.

Table 22. Secondary objective 5a. Descriptive statistics for time to an incident MACE event in Denmark.

	All Nocdurna ® patients	**Nocdurna ®, Male**	**Nocdurna ®, Female**	**All LUTS patients**	**LUTS, Male**	**LUTS, Female**
Time to cardiovascular death(days)						
N	10	7	3	30	20	10
Mean (SD)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)
Median	62.05	63.13	62.05	63.13	62.05	63.13
Range	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0
Interquartile ranges	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0
Missing values	0	0	0	0	0	0

SOURCE DOCUMENT: DEMOGRAPHY_MACE.SAS GENERATED: 22:53:48 16SEP2013 DB version DEV: ART_03, USER_ID LAJ.

Table 23. Secondary objective 5a. Incidence of major venous thromboembolic events in *country*.

Repeat Table 9 with major venous thromboembolic events as outcome

Figure 19. Secondary objective 5b. A Cox regression showing time to first major venous thromboembolic events stratified by patient group and age class in *country*.

Table 24. Secondary objective 5b. Incidence of major venous thromboembolic events divided in fatal and non-fatal events in Denmark and Sweden.

Repeat Table 9 with major venous thromboembolic events as outcome and with the double number of rows to account for the divided outcome (fatal and non-fatal).

Table 25. Secondary objective 5b. Descriptive statistics of time to hospital intensive care for VTE and time to death with VTE in Sweden.

Time to hospital intensive care	All Nocdurna ® patients	Nocdurna ®, Male	Nocdurna ®, Female	All LUTS patients	LUTS, Male	LUTS, Female
Time to hospital intensive care (days)						
N	23	10	13	50	30	20
Mean (SD)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)
Median	62.05	63.13	62.05	63.13	62.05	63.13
Range	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0
Interquartile ranges	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0
Missing values	0	0	0	0	0	0
Time to cardiovascular death(days)						
N	10	7	3	30	20	10
Mean (SD)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)
Median	62.05	63.13	62.05	63.13	62.05	63.13
Range	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0
Interquartile ranges	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0
Missing values	0	0	0	0	0	0

SOURCE DOCUMENT: DEMOGRAPHY_VTE.SAS GENERATED: 22:53:48 16SEP2013 DB version DEV: ART_03, USER_ID LAJ.

Table 26. Secondary objective 5b. Descriptive statistics for time to VTE as reason for death in Denmark.

	All Nocdurna ® patients	Nocdurna ®, Male	Nocdurna ®, Female	All LUTS patients	LUTS, Male	LUTS, Female
Time to cardiovascular death(days)						
N	10	7	3	30	20	10
Mean (SD)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)	61.17 (8.36)	62.81 (9.00)
Median	62.05	63.13	62.05	63.13	62.05	63.13
Range	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0	44.7 , 82.3	40.0 , 85.0
Interquartile ranges	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0	56.0 , 74.0	55.0 , 75.0
Missing values	0	0	0	0	0	0

SOURCE DOCUMENT: DEMOGRAPHY_VTEDeath.SAS GENERATED: 22:53:48 16SEP2013 DB version DEV: ART_03, USER_ID LAJ.

Table 27. Secondary objective 6. Incidence of acute exacerbation of congestive heart failure in *country* in a smaller population chronic cardiac insufficiency.

Repeat Table 9 with acute exacerbation of congestive heart failure as outcome but using the small population chronic cardiac insufficiency...

Table 28. Secondary objective 6. Demographic and health characteristics in *country* in a smaller population with chronic cardiac insufficiency.

Repeat Table 10 but in a smaller population chronic cardiac insufficiency.

Figure 20. Secondary objective 6. A Cox regression showing time to acute exacerbation of congestive heart failure events stratified by patient group and age class in *country*, but in a smaller population with chronic cardiac insufficiency.

Table 29. Secondary objective 7. Comparative analyses for Incidence of symptomatic hyponatraemia in *country*.

	Comparing		
Group and time period	IRR	95% CI	p-value
All time periods, all sub-populations			
Nocdurna ® compared with LUTS	xx.xx	(xx.xx , xx.xx)	0.xxxx
65-74 years compared with <65 y	xx.xx	(xx.xx , xx.xx)	0.xxxx
>=75 years compared with <65 y	xx.xx	(xx.xx , xx.xx)	0.xxxx
Males compared with females	xx.xx	(xx.xx , xx.xx)	0.xxxx
Scale – one value for each model	xx.xx		
Events first month after Index date, all sub-populations			
Nocdurna ® compared with LUTS	xx.xx	(xx.xx , xx.xx)	0.xxxx
65-74 years compared with <65 y	xx.xx	(xx.xx , xx.xx)	0.xxxx
>=75 years compared with <65 y	xx.xx	(xx.xx , xx.xx)	0.xxxx
Males compared with females	xx.xx	(xx.xx , xx.xx)	0.xxxx
Scale – one value for each model	xx.xx		
Events after first month and onwards, all sub-populations			
Nocdurna ® compared with LUTS	xx.xx	(xx.xx , xx.xx)	0.xxxx
65-74 years compared with <65 y	xx.xx	(xx.xx , xx.xx)	0.xxxx
>=75 years compared with <65 y	xx.xx	(xx.xx , xx.xx)	0.xxxx
Males compared with females	xx.xx	(xx.xx , xx.xx)	0.xxxx
Scale – one value for each model	xx.xx		

For incidence rates see **Table 9**. IRR= Incidence Rate Ratio: Ratio of IR to that of Control, where the controls are LUTS, <65 y age and females as indicated in the rows.
SOURCE DOCUMENT: Compare_prim.SAS GENERATED: 22:53:48 16SEP2021 DB version DEV: ART_03, USER_ID LAJ.

Table 30. Secondary objective 7. Comparative analyses for incidence of hyponatraemia requiring hospital intensive care in *Sweden*.

Repeat Table 29, with incidence of hyponatraemia requiring hospital intensive care in *Sweden* as outcome.

Table 31. Secondary objective 7. Comparative analyses for incidence of clinically significant hyponatraemia in *Denmark*.

Repeat Table 29, with changed for incidence of clinically significant hyponatraemia in *Denmark* as outcome.

Table 32. Secondary objective 7. Comparative analyses for all-cause mortality in *country*.

Repeat Table 29, with all-cause mortality as outcome.

Table 33. Secondary objective 7. Comparative analyses for incidence of major cardiovascular events in *country*.

Repeat Table 29, with for incidence of major cardiovascular events as outcome.

Table 34. Secondary objective 7. Comparative analyses for incidence of major venous thromboembolic events in *country*.

Repeat Table 29, with incidence of major venous thromboembolic events as outcome.

Table 35. Secondary objective 7. Comparative analyses for incidence of major venous thromboembolic events in *country.*

Repeat Table 29, with incidence of major venous thromboembolic events as outcome.

Table 36. Secondary objective 7. Comparative analyses for incidence of acute exacerbation of congestive heart failure in *country.*

Repeat Table 29, with incidence of acute exacerbation of congestive heart failure as outcome.

Table 37. Secondary objective 8. Cardiovascular and thromboembolic events resulting in treatment withdrawal in *Sweden*. Nocdurna ® patients only.

Repeat Table 29, with cardiovascular and thromboembolic events measured at the ICU wards in Sweden as outcome.

Incidence rate stratified according to label by proxy.

Table 38. Secondary objective 9. Incidence of symptomatic hyponatraemia in *country* for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients

	Nocdurna ® without contraindica-tion	**Nocdurna ®, Male**	**Nocdurna ®, Female**	**Nocdurna ® with contraindica-tion**	**Nocdurna ® , Male**	**Nocdurna ® , Female**
Variable, time period and population						
All patients - All exposure time						
Number of subjects	3512	2289	1223	1488	931	557
Number of events	493	367	126	129	93	36
Total person years (y)	510.4	335.7	174.7	219.5	138.4	81.0
Mean unadjusted rate of events (events/1000 person-years)	1201.8	1364.8	896.9	759.7	866.9	580.5
Variance of unadjusted rate	655.1	658.2	648.5	660.6	682.9	623.6
Number of patients with more than 1 event	29	25	4	8	5	3
Number of events in patients with more than 1 event	60	52	8	16	10	6
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx
Incidence rate (95 % CI)	861.40 (798.94 - 928.74)	1073.58 (989.55 - 1164.75)	688.70 (608.23 - 779.81)	532.61 (466.19 - 608.49)	662.92 (565.25 - 777.46)	427.68 (341.35 - 535.85)
Standard Error of Mean	33.08	44.64	43.66	36.19	53.91	49.20
Scale - one value for each model	0.7468	0.7796	0.6830			
Events first month after Index date						
Number of subjects	3512	2289	1223	1488	931	557
Number of events	129	98	31	28	18	10
Total person years (y)	491.4	321.7	169.6	214.7	134.5	80.2
Mean unadjusted rate of events (events/1000 Person-years)	312.8	362.0	220.8	161.9	176.6	137.3
Variance of unadjusted rate	642.4	645.5	636.7	661.6	683.9	625.5
Number of patients with more than 1 event	.	.	.	1	1	.
Number of events in patients with more than 1 event	.	.	.	2	2	.
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx
Incidence rate (95 % CI)	221.51 (201.40 - 243.62)	285.44 (257.50 - 316.41)	163.73 (139.55 - 192.11)	112.50 (94.11 - 134.48)	126.37 (100.58 - 158.78)	114.02 (87.49 - 148.60)

Standard Error of Mean	10.75	15.00	13.35	10.24	14.72	15.41
Scale - one value for each model	0.4641	0.4882	0.4168			
Events after first month and onwards						
Number of subjects	2324	1536	788	1017	639	378
Number of events	229	169	60	58	44	14
Total person years (y)	406.1	268.8	137.3	179.2	113.6	65.6
Mean unadjusted rate of events (events/1000 Person-years)	650.5	720.6	513.7	366.3	415.8	282.7
Variance of unadjusted rate	611.2	610.4	613.6	603.0	619.4	575.3
Number of patients with more than 1 event	13	11	2	4	3	1
Number of events in patients with more than 1 event	26	22	4	8	6	2
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx
Incidence rate (95 % CI)	513.14 (465.63 - 565.51)	628.77 (565.80 - 698.74)	421.10 (359.52 - 493.23)	297.85 (249.79 - 355.15)	386.66 (314.79 - 474.93)	207.78 (151.08 - 285.75)
Standard Error of Mean	25.44	33.85	33.97	26.74	40.57	33.78
Scale - one value for each model	0.6639	0.6936	0.6043			
Patients >= 65 years						
Number of subjects	2435	1573	862	1038	650	388
Number of events	379	281	98	100	69	31
Total person years (y)	352.4	230.4	122.0	152.6	96.6	56.0
Mean unadjusted rate of events (events/1000 Person-years)	1332	1519	993	843	915	722
Variance of unadjusted rate	648	646	649	646	661	620
Number of patients with more than 1 event	22	19	3	7	4	3
Number of events in patients with more than 1 event	46	40	6	14	8	6
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx
Incidence rate (95 % CI)	994.08 (912.02 - 1083.53)	1225.03 (1115.13 - 1345.76)	801.29 (695.41 - 923.29)	616.35 (527.97 - 719.52)	725.40 (600.62 - 876.09)	555.75 (432.23 - 714.58)
Standard Error of Mean	43.70	58.75	57.94	48.67	69.86	71.28
Scale - one value for each model	0.7701	0.7995	0.7140			

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Table 39. Secondary objective 9. Incidence of hyponatraemia requiring hospital intensive care for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients in Sweden.

Repeat Table 38 with hyponatraemia requiring hospital intensive care as outcome in hospital intensive care for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients in Sweden.

Table 40. Secondary objective 9. Incidence of clinically significant hyponatraemia for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients in Denmark.

Repeat Table 38 with clinically significant hyponatraemia as outcome for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients in Denmark.

Table 41. Secondary objective 9. Incidence of all-cause mortality for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients

Repeat Table 38 with all-cause mortality as outcome for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients.

Table 42. Secondary objective 9. Incidence of major cardiovascular events for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients.

Repeat Table 38 with major cardiovascular events as outcome for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients.

Table 43. Secondary objective 9. Incidence of major venous thromboembolic events for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients.

Repeat Table 38 with major venous thromboembolic events as outcome for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients.

Table 44. Secondary objective 9. Incidence of acute exacerbation of congestive heart failure for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients.

Repeat Table 38 with acute exacerbation of congestive heart failure events as outcome for patients with and without contraindications for Nocdurna ® use. Only Nocdurna ® patients.

Sensitivity analysis, demographics are not repeated

Table 45. Sensitivity analysis. Incidence of symptomatic hyponatraemia in *country* with second prescription shifted to the end of the first.

Repeat Table 9 with incidence of symptomatic hyponatraemia in *country* with second prescription shifted to the end of the first as outcome.

Table 46. Sensitivity analysis. Incidence of hyponatraemia requiring hospital intensive care in *Sweden* with second prescription shifted to the end of the first.

Repeat Table 9 with Incidence of hyponatraemia requiring hospital intensive care in *Sweden* with second prescription shifted to the end of the first as outcome.

Table 47. Sensitivity analysis. Incidence of clinically significant hyponatraemia in *Denmark* with second prescription shifted to the end of the first.

Repeat Table 9 with incidence of clinically significant hyponatraemia in *country* with second prescription shifted to the end of the first as outcome.

Table 48. Sensitivity analysis. All-cause mortality in *country* with second prescription shifted to the end of the first.

Repeat Table 9 with all-cause mortality in *country* with second prescription shifted to the end of the first as outcome.

Table 49. Sensitivity analysis. Incidence of major cardiovascular events in *country* with second prescription shifted to the end of the first.

Repeat Table 9 with incidence of major cardiovascular events in *country* with second prescription shifted to the end of the first as outcome.

Table 50. Sensitivity analysis. Incidence of major venous thromboembolic events in *country* with second prescription shifted to the end of the first.

Repeat Table 9 with incidence of major venous thromboembolic events in *country* with second prescription shifted to the end of the first as outcome.

Table 51. Sensitivity analysis. Incidence of acute exacerbation of congestive heart failure in *country* with second prescription shifted to the end of the first.

Repeat Table 9 with incidence of acute exacerbation of congestive heart failure in *country* with second prescription shifted to the end of the first as outcome.

Table 52. Sensitivity analysis. Incidence of symptomatic hyponatraemia in *country* with prescribed intake used instead of 1 tablet per day in Denmark and Sweden, if possible. LUTS patients are unchanged.

Table 53. Sensitivity analysis. Incidence of hyponatraemia requiring hospital intensive care in Sweden with prescribed intake used instead of 1 tablet per day, if possible. LUTS patients are unchanged.

Table 54. Sensitivity analysis. Incidence of clinically significant hyponatraemia in *Denmark* with prescribed intake used instead of 1 tablet per day, if possible. LUTS patients are unchanged.

Table 55. Sensitivity analysis. All-cause mortality in *country* with prescribed intake used instead of 1 tablet per day in Denmark and Sweden, if possible. LUTS patients are unchanged.

Table 56. Sensitivity analysis. Incidence of major cardiovascular events in *country* with prescribed intake used instead of 1 tablet per day in Denmark and Sweden, if possible. LUTS patients are unchanged.

Table 57. Sensitivity analysis. Incidence of major venous thromboembolic events in *country* with prescribed intake used instead of 1 tablet per day in Denmark and Sweden, if possible. LUTS patients are unchanged.

Table 58. Sensitivity analysis. Incidence of acute exacerbation of congestive heart failure in *country* with prescribed intake used instead of 1 tablet per day in Denmark and Sweden, if possible. LUTS patients are unchanged.

Meta-analysis

Table 59. Meta-analysis. Combined demographic and health characteristics in the study.

	Nocdurna ®				LUTS			
	Denmark	Germany	Sweden	Overall	Denmark	Germany	Sweden	Overall
Age (year)								
N	Xx	X	Xx	Xx	Xx	Xx	Xx	Xx
Mean (SD)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Range	Xx, xx	Xx, xx	Xx, xx	Xx, xx	Xx, xx	Xx, xx	Xx, xx	Xx, xx
Missing values	x	x	x	x	x	x	x	x
Repeat above 7 lines for								
Number of hospitalisations	…							
Number of emergency room visits	…							
Gender, n and (%)								
Male	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Female	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)	Xx (xx)
Repeat the above 3 lines for								
Polyuria R35								
Diabetes mellitus; E10, E11, E12, E13 and E14								
Diabetes insipidus, E23.2								
Overactive bladder, N31.0, N31.2, N31.9, N39.4, R39.1 and ATC G04BD								
Benign prostatic hyperplasia, N40, D29.1 and ATC G04C								
Urinary tract infection, N39.0, N30, N10								
Polydipsia, R36.1								

Heart failure, I50

Hypertension, I10

Hyperlipidaemi, E78

Atrial fibrillation, I48

Obesity, E66

Kidney disease, N18, N19

Cystic fibrosis, E84

Pre-eclampsia, O11, O14

Chronic lung disease, J40-J47, J60-J70, J80, J82, J84, J95-J99

Liver disease, K70-K77, F10 and ATC N07BB

Cancer, C00-C43, C45-C97

Prostate cancer, C61

Bladder cancer, C67

Dementia F00, F01, F02, F03, F04, G30, G31.0, G31.1

Co-medication

Loperamide, A07DA03

Antidiabetics, A10

Sulfonylureas including chlorpropamide, A10BB

Amiodarone, C01BD01

Antihypertensives, C02

Diuretics, C03

Special diuretics, C03A, C03B, C03C, C03D and C03E

Beta blocking agents, C07

Special beta blocking agents, C07B, C07C and C07D

Calcium channel blockers and diuretics, C08G

ACE inhibitors, C09A

Special ACE inhibitors, C09BA

Angiotensin II receptor blockers, C09C

Angiotensin II receptor blockers (combinations), C09D

Lipid-modifying agents, C10

Vasopressin and analogues (incl. desmopressin), H01BA

Systemic corticosteroids, H02

Antiepileptics, N03A

Carbamazepine and lamotrigine, N03AF01 and N03AX09

Non-selective monoamine reuptake inhibitors, N06AA

Selective serotonin reuptake inhibitors, N06AB

Chlorpromazine, N05AA01

NSAIDs, M01A

Opioids, N02A

Phenothiazines with aliphatic side-chain, N05AA

Chlorpromazine, N05AA01	
Lithium, N05AN01	
Antidepressants, N06A	
Antiinflammatory agents, non-steroids , M01A	
Overactive bladder, G04BD	
Benign prostatic hyperplasia, G04C	
Desmopressin, H01BA02	
Patients >= 65 years	
Repeat all the above rows for this population	

Table 60. Meta-analysis. Incidence rates from the 3 countries and combined

Incidence rate for	**Nocdurna ®**				**LUTS**			
	Denmark	Germany	Sweden	Overall	Denmark	Germany	Sweden	Overall
Diagnose code for low NA levels	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)
All-cause mortality	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)
Major cardiovascular events	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)
Venous thromboembolic events	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)
Congestive heart failure	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)	XX (xx-xx)

Note: Incidence rate per 1000 person years are given together with 95% CI. SOURCE DOCUMENT: meta1.SAS GENERATED: 22:53:48 16JAN2021 DB version DEV: Simulated data, USERID: LAJ

Figure 21. Meta-analysis. A Galbraith to the left and a forest plot to the right illustrating the difference between the countries for incidence rate ratio of symptomatic hyponatraemia.

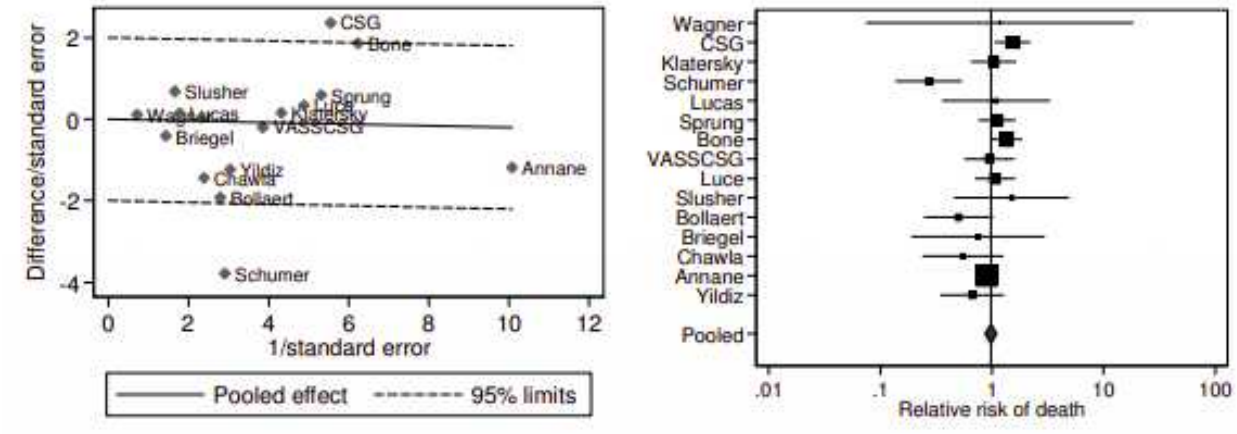
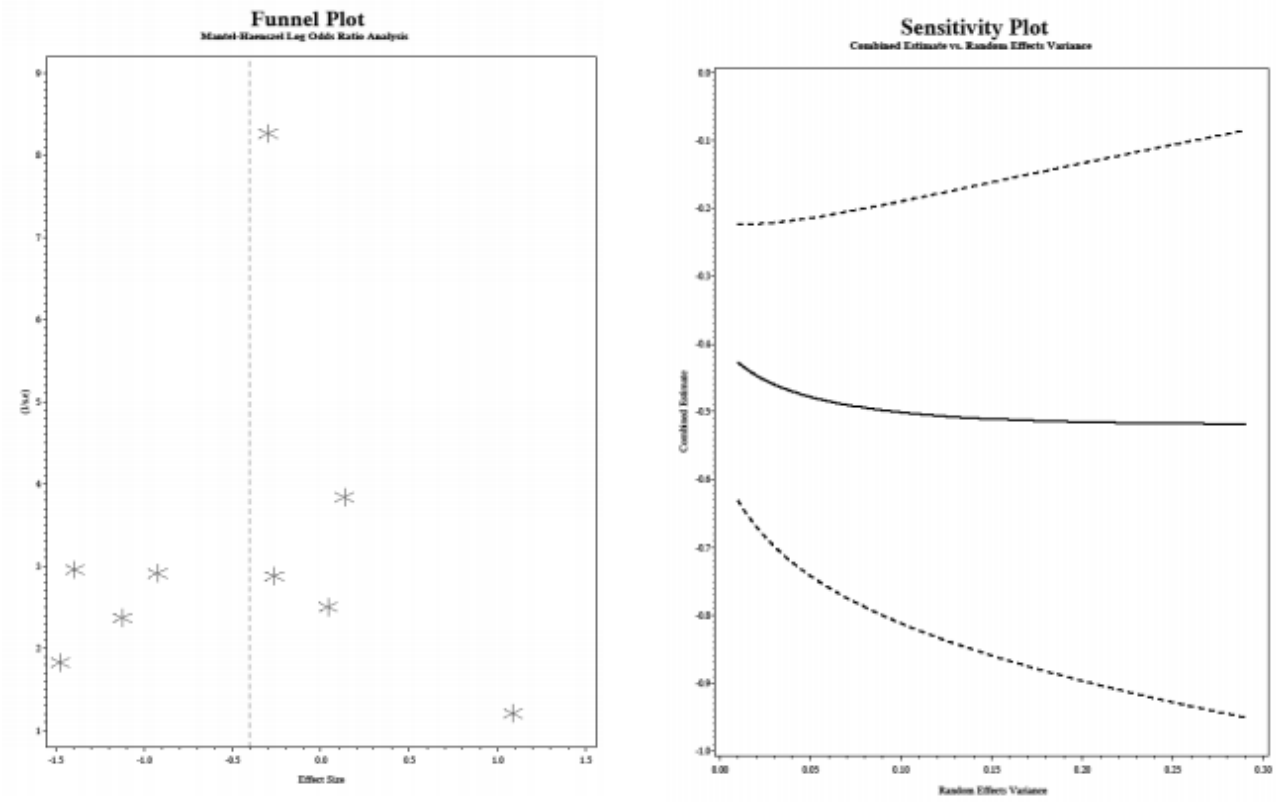


Figure 22. Meta-analysis. A funnel plot to the left and a sensitivity plot to the right for incidence rate ratio of symptomatic hyponatraemia.



In the sensitivity plot the gap between the 95% CI dotted curves is increasing indicating that a random effect model will have a larger confidence interval.

Table 61. Meta-analysis of the combined effect using random and fixed model and 7 different methods for incidence rate ratio of symptomatic hyponatraemia.

Model type	**Method**	**Estimate**	**Standard Error**	**Lower CL**	**Upper CL**
Fixed	Mantel Haenszel	Xx	Xx	Xx	xx
Fixed	Inverse variance weighting	Xx	Xx	Xx	xx
Fixed	*Logistic regression*	Xx	Xx	Xx	xx
Random	Der Simonian Laird	Xx	Xx	Xx	xx
Random	Hardy Thompson Wald	Xx	Xx	Xx	xx
Random	Hardy Thompson Profile			Xx	xx
Random	Normal Binomial mixture	Xx	Xx	Xx	xx

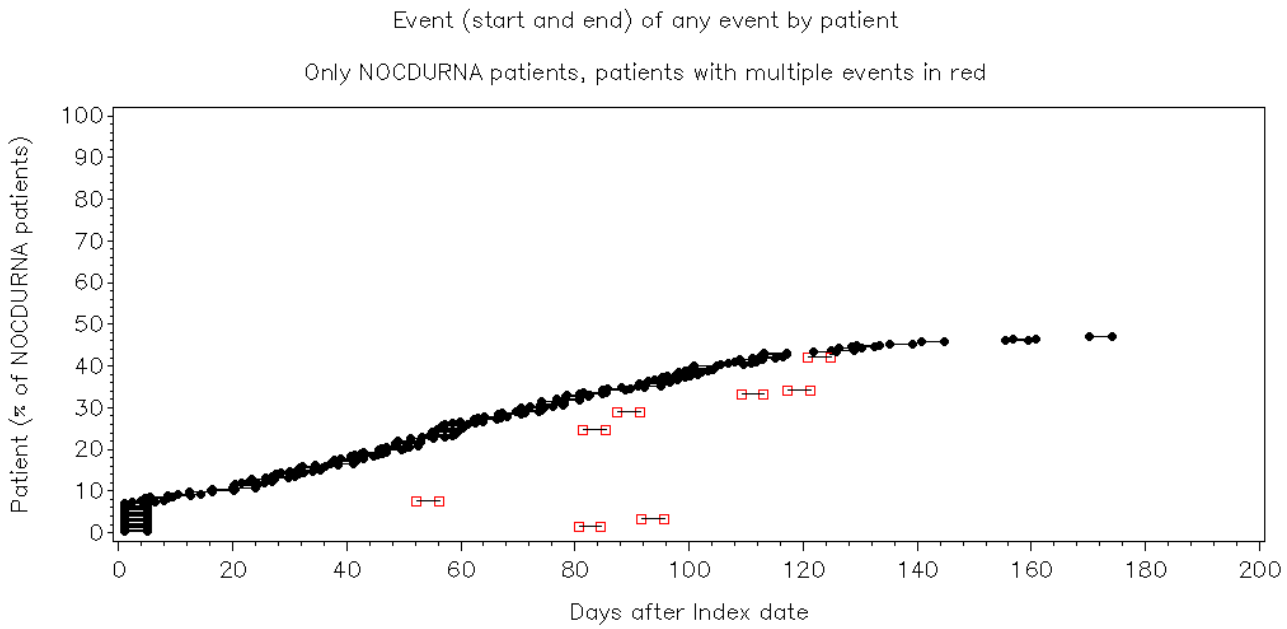
Observe that the *fixed logistic regression in italic* is the model suggested in the protocol. SOURCE DOCUMENT: meta_fixed.SAS GENERATED: 22:53:48 16JAN2021 DB version DEV: Simulated data, USERID: LAJ

Analysis of several events for each patient (Optional)

Table 66. Optional. Incidence of symptomatic hyponatraemia in country, if there are more than 5% of the patients that are having more than 1 event

Repeat Table 9, but with a changed regression taking into account that there are several events for more than 5% of the patients. The SAS macro must be re-programmed.

Figure 31. Optional. Survival curve, if there are more than 5% of the patients that are having more than 1 event.



Footnote: The SAS source code for the figure will be sent to BIPS/Statistics Denmark if needed.

15 REFERENCES

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16 APPENDICES

16.1 SAS macros

Two SAS macros will to do the main part of the analysis

A SAS macro has been developed to be used in the main part of the analysis have been develop. The macro is called NOCDURNA_MAC. There are several reasons for this approach.

1) It saves overall time used in the program development.

2) The Poisson regression in SAS is not doing any back transformation from the log transformation of the rates, so it is nice to have that done already.

3) It is expected that there will be differences in the rates between the different countries and when a common macro have been used, these differences must be found in other places than in the statistical analysis

4) The QC is simplified, since a potential error in the macro will be found/tested by at least 3 different persons. If an error/improvement is found the project manager and project statistician should be notified.

5) Less work for the statistician and more work for the programming teams.

The macro is performing the main Poisson regression for rate calculation as specified in the SAP, and this macro should be used in the primary objective, and the secondary objectives 2, 3, 4, 5a, 5b, 6, 8, and 9. Secondary objective 9 will need minor output corrections, but the main part of the analysis can be done by the NOCDURNA_MAC macro.

The overall principle in developing the macro has been to keep the SAS programming simple and easy to understand. Shortcuts to make the output elegant has been avoided. Also the listing has not been turned off, so the LOG-file can be inspected. There are no loops for resetting or testing if the input is valid, and there are no clean-up for deleting datasets that have been used during the macro

Runtime error might be expected where there are zero events and where the Poisson model cannot converge, but an early graphical output inside the macro should be able to find these cases and during test runs with zero events the macro has executed without errors. If the Poisson regression is unable to converge, the mean unadjusted events rates will be used in the interpretation of the results.

The macro call is

```
%NOCDURNA_MAC(baseline=baseline, eventdata=eventdata,
compare=compare,out_table=out_table,dir=dir,ttitle=ttitle);
```

The overall idea is to create two datasets, one with all patients and their characteristics, and another dataset with all events and the characteristics of the events. The macro will write to a word compatible file (a RFT – file) and the output place of the file and the title of the generated table must be specified in the macro call.

Figure 32. Data flow in the SAS macros for Poisson regression.

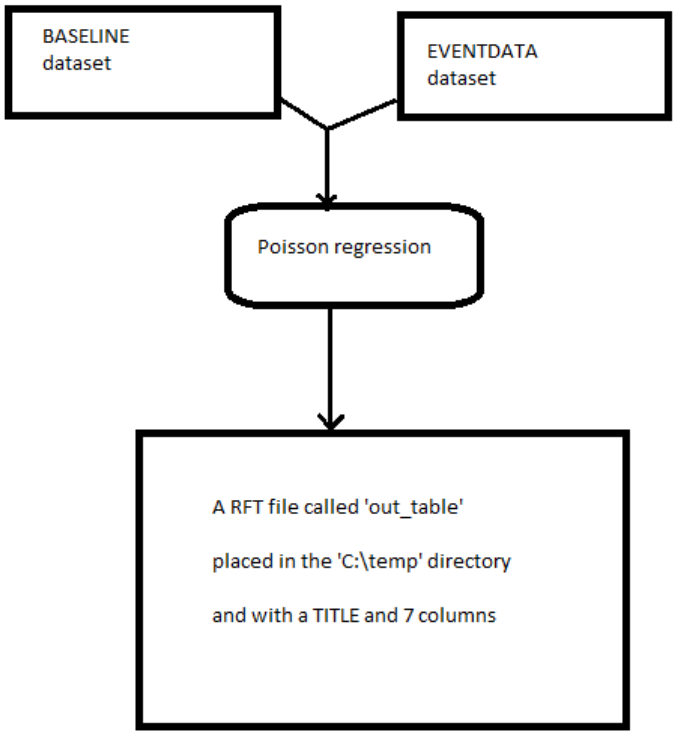

Table 67. Description of the input datasets. The baseline dataset must contain only one observation for each patient

Variable	Type	Length	Description
Patent_id	Num	8	A unique value for each patient
Class	Char	9	LUTS or NOCDURNA, LUTS can be changed to a variable in secondary objective 9.
gender	Char	1	Gender, F or M
exposure	Num	8	Length of exposure time in study, from index date to end of study, in days

Log_exposure	Num	8	Natural log function of exposure in log(days)
Age_class	Num	12	Age classified in ' <65 years ', '65-74 years' and '>=75 years '. Don't forget the space/blank in front of 'B<65 years ' to get the right sorting

Below is a partial listing of the dataset

Obs	class	age_class	gender	exposure	log_ exposure	patient_ id
3025	NOCDURNA	>=75 years	F	44.3876	3.79296	3025
3026	LUTS	65-74 years	F	36.8901	3.60794	3026
3027	NOCDURNA	65-74 years	M	50.8905	3.92968	3027
3028	LUTS	<65 years	M	80.8589	4.39271	3028

The events dataset must have one observation for each event. Each patient can have several observations if the patient has several events. An unlimited number of events are possible for each patient. There are 3 variables in the Eventdata dataset

Table 68. Description of the input Eventdata. There can be several events for each patient

Variable	Type	Length	Description
Patent_id	Num	8	A unique value for each patient
Time_to_event	Num	8	Time in days between index date and date of event
Event_one	Num	1	Equal to one when there is an event, useful in further calculation.

Below is a partial listing of the dataset

Obs	patient_ id	TIME_TO_ EVENT	event_ one
37	318	38.993	1
38	318	83.672	1
39	355	57.820	1
40	364	1.000	1
41	367	81.453	1

Please observe that the patient with patient_id = 318 has 2 events, one after 38 days and another after 83 days. The decimals in the variable time_to_event is due to the synthetic nature of the data.

There are 3 variables to specify the output for the macro, one for the table, one for the directory and one for the table and figure title.

The SAS macro was:

%NOCDURNA_MAC(baseline=baseline,eventdata=eventdata,compare=LUTS,out_table=out_table,dir=dir,ttitle=ttitle);

The 'LUTS' value in the macro can be changed to e.g. 'Off label' when objective 9 is analysed. Please check that the columns are in the correct order in the output and not interchanged.

The SAS macro variable 'DIR' gives a reference to the directory where the RTF table is written, in the development case, the 'C:\temp' directory have been specified, but each site will have a designated directory for the output. Please observe that there is no ending '\' in this macro variable.

The last SAS macro variable 'TTITLE' gives both the headline of the table and the headline (title) of the figure generated inside the SAS macro. Please do not use any ',' inside the text string specified in the macro call.

That is all for the input datasets.

Calculations inside the macro.

The Poisson regression is performed and a calculation is used to calculate the yearly rates. This is the key analysis.

```
ods output  ParameterEstimates=ParameterEstimates;
proc genmod data=to_poisson;
class class gender age_class;
model events  =  class age_class gender   / dist=poisson link=log
offset=log_exposure   scale=d  type3;
store p1;
run;
ods output lsmeans=lsmeans;
proc plm source = p1;
  lsmeans class /ilink cl;
run;
quit;
```

The 'STORE P1' is generating data that can be used for post analysis calculations, in this case will the 'PROC PLM' use the 'P1' data collection.

After the yearly rate per 1000 patient years are calculated and merged together with the rest of the analysis and a 'PROC REPORT' is used for writing the output RTF file.

When the macro is run several time, be sure to exit the Word document between different runs of the SAS macro, if not the output file will be locked and SAS will not be able to write to the file.

16.2 Another macro

A macro is also developed for doing the analysis in objective 7 comparing the incidence rate ratios between the treatments (Nocdurna ® and LUTS) taking confounding factors into the analysis. The confounding factors are age class and gender.

That macro is called NOCDURNA_MAC7 (the 7 reflecting objective 7) and has the basic data flow and the same input datasets. Once the datasets for the Poisson regression are created this macro just needs to be called for doing the analysis described in objective 7. This macro should not be used for analysing objective 9.

16.3 Programming left to be done for analysing outcome

A program for study objective 2 with descriptive analysis of baseline characteristics has not been developed. It is expected that the institutions already are have standard software for this analysis adapted to the variable names and values in the databases.

The SAS boxplots, symmetry plots, normal quantile plots and normal probability plots also need to be generated. The PLOT statement in PROC UNIVARIATE will generate the Boxplot. The normal probability plots will be generated with PROBPLOT statement in PROC UNIVARIATE. The PROC UNIVARIATE with a QQPLOT statement will generate the normal quantile plots. Finally, the symmetry plot will be generated by the HISTOGRAM / NORMAL statement in PROC UNIVARIATE. The final appearance of the figures will depend on the actual data and the axe are difficult to determinate before the first interim analysis. Examples of some of these figures can be found in the SAS PROC UNIVARIATE documentation and in (Dennis et al., 2019)

The Cox regression is not included. Please add the 'PLOTS=SURVIVAL' and a 'CLASS treatment group' to the SAS statement in the 'PROC PHREG' procedure.

Also the COX regression used in the case if more than 5% of the patients are having more than 1 event are not included, but there is a reference in the SAS example. SAS code for generating **Figure 31** will be provided by Statistician PPD .

16.4 Meta-analysis

In the final report planned for December 2023 a meta-analysis will be done. The meta-analysis is planned for Q3 in 2023. Combining incidence rates and descriptive statistics are described in the text, but the programming meta-analysis of the incidence rate ratios is described below.

A suite of SAS macros have been developed to do this task sponsored by Novartis. These macros will be applied.

Table 69. Description of SAS macros used for meta-analysis

Macro name	Description	Link
Mabinary	To carry out various approaches to analyzing binary data including classic Mantel-Haenszel analysis but also, for example, the analysis of Normal-binomial mixtures using PROC NLMIXED	mabinary.sas
maforest	To produce so-called forest plots whereby individual trials are represented by horizontal lines joining lower and upper confidence limits with a plotting symbol for the estimate and a final line and symbol for the overall meta-analytic summary	maforest.sas
mafunnel	To produce funnel plots. These plot the treatment estimate on the horizontal axis and the reciprocal of the standard error of the treatment estimate on the vertical axis.	mafunnel.sas
magalbraith	To produce radial or Galbraith plots as described in *Statistics in Medicine*, 1988.**7**,889-894. These plot the Z-scores, that is to say the ratio of estimated treatment effect to standard error, against the reciprocal of the standard error, where the latter is calculated as for a fixed effects analysis.	magalbraith.sas
mainverse	To carry out classic fixed effects meta-analysis using inverse weighting by variances of treatment contrasts.	mainverse.sas
mapeterlee	To implement Lee's checks as described in *Statistics in Medicine*,1999**,18**,1973-1981.	mapeterlee.sas
maqq	To produce QQ plots of estimated treatment effects by trial.	maqq.sas
marandom	To carry out random effects analysis using the approach of DerSimonian and Laird (DSL), *Controlled Clinical Trials*, 1986,**7**,177-188 and also using that of Hardy and Thompson(HT), *Statistics in Medicine*, 1996,**15**, 619-629.	marandom.sas
masensitivity	To examine the sensitivity of conclusions from random effects analysis to the magnitude of the random effects variance.	masensitivity.sas

There is also a sample program for showing the correct usage of the macros.

16.5 ICD 10 and ATC codes used in the study

Definitions of the LUTS cohort, outcome events and covariates

Table 70. ATC codes used to define the LUTS cohort

Characteristic	ATC code	Description
Overactive bladder	G04BD	Drugs for urinary frequency and incontinence
Benign prostatic hyperplasia	G04C	Drugs used in benign prostatic hypertrophy

Copied from protocol

Table 71. Codes used to define subpopulations, e.g. the contraindications for Nocdurna ® usage.

Characteristic	ICD-10 code	Description
Hyponatraemia	E87.1	
Polydipsia	R63.1	
Congestive heart failure	I50	Heart failure (all subcodes included)
Chronic kidney disease	N18.3	Chronic kidney disease, stage 3 (moderate)
	N18.4	Chronic kidney disease, stage 4 (severe)
	N18.5	Chronic kidney disease, stage 5
	N18.6	End stage renal disease
Syndrome of inappropriate antidiuretic hormone secretion	E22.2	

Updated from protocol

Table 72. Codes used to define outcome events

Outcome	ICD-10 code	Description
Hyponatremia		
Hyponatraemia	E87.1	
Hyponatremia (biochemical definition)	n/a	Will be ascertained using biochemical definition: serum sodium concentration <135 mmol/L (mild hyponatraemia) *Evaluated only in Denmark*
Major cardiovascular events (MACE)		
Myocardial infarction	I21, I22	
Stroke, ischemic	I63.3-I63.9, I66	
Major venous thromboembolic events		
Pulmonary embolism	I26	
Deep vein thrombosis	I80.1–I80.9	
Portal vein thrombosis	I81	
Mortality		
All-cause mortality	Any	Death from any cause
Heart failure		
Heart failure	I50	

Copied from protocol

Table 73. Codes used to define covariates

Covariate	ICD-10 code	ATC code	Description/comment
Comorbidities			
History of hyponatraemia, MACE and VTE	Please refer to Table 72		
Polyuria	R35		Polyuria
Diabetes mellitus	E10		Type 1 diabetes mellitus
	E11		Type 2 diabetes mellitus
	E12		Malnutrition-related diabetes mellitus
	E13		Other specified diabetes mellitus
	E14		Unspecified diabetes mellitus
Diabetes insipidus	E23.2		
Overactive bladder	N31.0		Uninhibited neuropathic bladder, not elsewhere classified
	N31.2		Flaccid neuropathic bladder, not elsewhere classified
	N31.9		Neuromuscular dysfunction of bladder, unspecified
	N39.4		Other specified urinary incontinence
	R39.1		Other difficulties with micturition
		G04BD	Drugs for urinary frequency and incontinence
Benign prostatic hyperplasia	N40		Benign prostatic hyperplasia
	D29.1		Benign neoplasm of prostate
		G04C	Drugs used in benign prostatic hypertrophy
Urinary tract infection	N39.0		Urinary tract infection, site not specified
	N30		Cystitis
	N10		Acute tubulo-interstitial nephritis
Polydipsia	R36.1		Excessive thirst
Heart failure	I50		
Hypertension	I10		Essential (primary) hypertension; medications to

			be used as proxy (see below under co-medications)
Hyperlipidaemia	E78		Disorders of lipoprotein metabolism and other lipidaemias; medications to be used as proxy (see below under co-medications)
Atrial fibrillation	I48		
Obesity	E66		
Kidney disease	N18		
	N19		
Cystic fibrosis	E84		
Pre-eclampsia	O11		Pre-eclampsia superimposed on chronic hypertension
	O14		Pre-eclampsia
Chronic lung disease	J40-J47		Chronic lower respiratory diseases
	J60-J70		Lung diseases due to external agents
	J80		Adult respiratory distress syndrome
	J82		Pulmonary eosinophilia, not elsewhere classified
	J84		Other interstitial pulmonary diseases
	J95-J99		Other diseases of the respiratory system
Liver disease	K70-K77		Diseases of liver
	F10	N07BB	F10 (mental and behavioural disorders due to use of alcohol) and N07BB (drugs used in alcohol dependence) included as proxy measures of liver disease
Cancer	C00-C43		Cancer excluding non-melanoma skin cancer
	C45-C97		C61 (prostate cancer) and C67 (bladder cancer) of special interest
Dementia	F00		Dementia in Alzheimer disease

	F01	Vascular dementia
	F02	Dementia in other diseases classified elsewhere
	F03	Unspecified dementia
	F04	Organic amnesic syndrome, not induced by alcohol and other psychoactive substances
	G30	Alzheimer's disease
	G31.0	Frontotemporal dementia
	G31.1	Senile degeneration of the brain
Number of hospitalisations	Any	Marker of overall health; to be assessed in the year before the index date
Number of emergency room visits	Any	Marker of overall health; to be assessed in the year before the index date
Co-medications, including drugs that may increase the risk of hyponatraemia		
Loperamide	A07DA03	
Antidiabetics	A10	A10BB (sulfonylureas including chlorpropamide), of special interest
Amiodarone	C01BD01	
Antihypertensives	C02	
Diuretics	C03	C03A, C03B, C03C, C03D and C03E of special interest
Beta blocking agents	C07	C07B, C07C and C07D of special interest
Calcium channel blockers and diuretics	C08G	
ACE inhibitors	C09A	C09BA of special interest
Angiotensin II receptor blockers	C09C	
Angiotensin II receptor blockers (combinations)	C09D	C09DA of special interest
Lipid-modifying agents	C10	
Vasopressin and analogues (incl. desmopressin)	H01BA	
Systemic corticosteroids	H02	
Antiepileptics	N03A	N03AF01 (carbamazepine) and N03AX09 (lamotrigine) of special interest

Non-selective monoamine reuptake inhibitors	N06AA	
Selective serotonin reuptake inhibitors	N06AB	
Chlorpromazine	N05AA01	
NSAIDs	M01A	
Opioids	N02A	
Phenothiazines with aliphatic side-chain	N05AA	N05AA01 (chlorpromazine) of special interest
Lithium	N05AN01	
Antidepressants	N06A	
Antiinflammatory agents, non-steroids	M01A	

Copied from protocol

STATISTICAL ANALYSIS PLAN

AMENDMENT 1

POST AUTHORISATION SAFETY STUDY (PASS), SAP

Post-authorisation safety study of NOCDURNA for the symptomatic treatment of nocturia due to idiopathic nocturnal polyuria: A multi-country cohort study using secondary data

000248

Investigational Product: Desmopressin, one oral lyophilisate per day

Indication: N/A

Phase: IV

Author: PPD

Date of issue: 11th of November 2022

Version: 1.0

Change log

Version No.	Effective Date	Reason for the Change / Revision	Supersedes
AMENDMENT 1	11 November 2022	EMA has required one additional sensitivity analysis to be performed included in the next reports.	N/A

Review and Approval of Amendment to Statistical Analysis Plan

Author:

PPD

Reviewers:

PPD

PPD

PPD

PPD

PPD

Approval by (e-signed in REAL):

PPD

TABLE OF CONTENTS

List of Tables

1 INTRODUCTION

This document describes the additional analysis to be conducted as suggested by EMA Läkemedelsverket in the Type II variation Final Variation Assessment Report on use of Nocdurna with the reference code SE/H/1507/01-02/II/12.

2 REASON FOR ADMENDMENT

This study defines two study populations, a NOCDURNA population and a LUTS population. All patients that are treated with NOCDURNA are defined as a part of the NOCDURNA population, independently of any treatment with LUTS defining drugs. Since there is a degree of overlap between the two populations, some patients will be using both NOCDURNA and LUTS drugs. The protocol and statistical analysis plan clearly defines these patients to be analysed as NOCDURNA patients.

In the Final Variation Assessment Report of the first interim report in this study EMA had the following comment: *The MAH should further discuss the impact of including patients treated with both drugs into the Nocdurna group and consider performing sensitivity analysis with the combination treatment group separated.*

This amendment describe the analysis suggested by EMA.

This amendment will assure a common implementation of the additional sensitivity analysis in the three countries.

3 ANALYSIS SET

In the original statistical analysis plan a new section will be added with the number 5.1.8 on page 20 in the pdf version of the Statistical Analysis Plan stored in REAL (Ferring document management system) dated the 18th of August 2021.

'5.1.8'.

The new treatment groups will be defined in the following.

The protocol specifies in section 9.2 the inclusion and exclusion criteria for the NOCDURNA and LUTS patients and the patients must fulfil these conditions. The extra analysis will divide these patients into three groups where the two first groups will be a division of the NOCDURNA cohort.

1) The *combination group* also called *'NOCDURNA and LUTS treated'* of patients must have initiated NOCDURNA treatment at any time during the study period and also a LUTS treatment must have been initiated during the study period.

2) The NOCDURNA patients not included in the combination group also called the '*Only NOCDURNA treated*' must have initiated the NOCDURNA at any time during the study period, but not have initiated a LUTS treatment during the study period.

3) The patients not included in 1) or 2) above should have initiated a LUTS treatment, but not a NOCDURNA treatment during the study period.

The order of the initialization of the treatments are not considered, and there is no condition about the treatments should be overlapping in time.

The analysis of the events will calculate the incidence rates of the patients in group 1 and 2.

The number of patients in '*NOCDURNA and LUTS treated'* and '*Only NOCDURNA treated'* are presented in the first interim report in table 22 for Sweden and in table 58 for Denmark. There were in total 1606 NOCDURNA patients in Sweden and 741 NOCDURNA patients in Denmark in the first year and the combination group was 63.5% in Sweden and 65.7% in Denmark.

4 ADDITIONAL SENSITIVITY ANALYSIS

In the original statistical analysis plan a new section will be added into the section with the number '10.1.3 SENSITIVITY ANALYSIS' on page 29 in the pdf version of the Statistical Analysis Plan stored in REAL dated the 18th of August 2021.

'10.1.3'.

An additional sensitivity analysis will be performed analysing NOCDURNA patients divided into two groups, one group defined as 'Only NOCDURNA treated' and the other group as 'NOCDURNA and LUTS treated'. The analysis will be done as described in section 10.1.2 Incidence of symptomatic hyponatraemia' on page 27 in the pdf version of the Statistical Analysis Plan stored in REAL dated the 18th of August 2021. The section describing the analysis is cited below to make this a stand-alone document. Only the primary objective of symptomatic hyponatraemia will be analysed in this sensitivity analysis.

> 'The incidence rate of the primary outcome reported since index date in the study period will be modelled using a Poisson regression model and expressed as number of cases per 1000 patients years at risk (+- 95% CI) for the Nocdurna ® group and the LUTS contextual cohort, separately. Person-period at risk is defined according to person-time observed from the index date to the first right censoring event. The dependent variable will be number of events for each person and the independent variable will be treatment, age class, and gender. Stratum-specific incidence rates will also be examined giving rates divided by gender, first month after index date and events occurring after the first month after the index date. Also incidence rates for patients with an age above or equal to 65 years will be calculated.'

5 TABLE SHELL

All number in the table are random numbers.

Table 1A extra Sensitivity analysis. High level results of Incidence of symptomatic hyponatraemia in *country*

	Only NOCDURNA treated	Only NOCDURNA treated, Male	Only NOCDUR-NA treated, Female	NOCDURNA and LUTS treated	NOCDURNA and LUTS treated, Male	NOCDURNA and LUTS treated, Female	**NOC-DURNA, M+F**	**NOCDURNA, Male**	**NOC-DURNA, Female**
Number of subjects	663	141	522	943	382	561	1606	523	1083
Number of events	4	1	3	10	3	7	14	4	10
Mean unadjusted rate of events	14.92	16.00	14.59	23.12	17.22	27.10	19.98	16.90	21.56
Incidence rate	11.18	N/A	N/A	18.01	N/A	N/A	13.65	13.97	14.45
[95 % CI]	[8.13; 15.36]			[14.32; 22.65]			[12.07; 15.43]	[11.12;17.55]	[12.49;16.71]

Table 2A extra Sensitivity analysis. Incidence of symptomatic hyponatraemia in *country*

	Only NOCDURNA treated	Only NOCDURNA treated, Male	Only NOCDURNA treated, Female	NOCDURNA and LUTS treated	NOCDURNA and LUTS treated, Male	NOCDURNA and LUTS treated, Female
Variable, time period and population						
All patients - All exposure time						
Number of subjects	3512	2289	1223	1488	931	557
Number of events	493	367	126	129	93	36
Total person years (y)	510.4	335.7	174.7	219.5	138.4	81.0
Mean unadjusted rate of events (events/1000 person-years)	1201.8	1364.8	896.9	759.7	866.9	580.5
Number of patients with more than 1 event	29	25	4	8	5	3
Number of events in patients with more than 1 event	60	52	8	16	10	6
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx

	Only NOCDURNA treated	Only NOCDURNA treated, Male	Only NOCDURNA treated, Female	NOCDURNA and LUTS treated	NOCDURNA and LUTS treated, Male	NOCDURNA and LUTS treated, Female
Incidence rate (95 % CI)	861.40 (798.94 - 928.74)	1073.58 (989.55 - 1164.75)	688.70 (608.23 - 779.81)	532.61 (466.19 - 608.49)	662.92 (565.25 - 777.46)	427.68 (341.35 - 535.85)
Standard Error of Mean	33.08	44.64	43.66	36.19	53.91	49.20
Scale - one value for each model	0.7468	0.7796	0.6830			
Events first month after Index date						
Number of subjects	3512	2289	1223	1488	931	557
Number of events	129	98	31	28	18	10
Total person years (y)	491.4	321.7	169.6	214.7	134.5	80.2
Mean unadjusted rate of events (events/1000 person-years)	312.8	362.0	220.8	161.9	176.6	137.3
Variance of unadjusted rate	642.4	645.5	636.7	661.6	683.9	625.5
Number of patients with more than 1 event	.	.	.	1	1	.
Number of events in patients with more than 1 event	.	.	.	2	2	.
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx
Incidence rate (95 % CI)	221.51 (201.40 - 243.62)	285.44 (257.50 - 316.41)	163.73 (139.55 - 192.11)	112.50 (94.11 - 134.48)	126.37 (100.58 - 158.78)	114.02 (87.49 - 148.60)
Standard Error of Mean	10.75	15.00	13.35	10.24	14.72	15.41
Scale - one value for each model	0.4641	0.4882	0.4168			
Events after first month and onwards						
Number of subjects	2324	1536	788	1017	639	378
Number of events	229	169	60	58	44	14
Total person years (y)	406.1	268.8	137.3	179.2	113.6	65.6
Mean unadjusted rate of events (events/1000 person-years)	650.5	720.6	513.7	366.3	415.8	282.7
Variance of unadjusted rate	611.2	610.4	613.6	603.0	619.4	575.3
Number of patients with more than 1 event	13	11	2	4	3	1

	Only NOCDURNA treated	Only NOCDURNA treated, Male	Only NOCDURNA treated, Female	NOCDURNA and LUTS treated	NOCDURNA and LUTS treated, Male	NOCDURNA and LUTS treated, Female
Number of events in patients with more than 1 event	26	22	4	8	6	2
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx
Incidence rate (95 % CI)	513.14 (465.63 - 565.51)	628.77 (565.80 - 698.74)	421.10 (359.52 - 493.23)	297.85 (249.79 - 355.15)	386.66 (314.79 - 474.93)	207.78 (151.08 - 285.75)
Standard Error of Mean	25.44	33.85	33.97	26.74	40.57	33.78
Scale - one value for each model	0.6639	0.6936	0.6043			
Patients >= 65 years						
Number of subjects	2435	1573	862	1038	650	388
Number of events	379	281	98	100	69	31
Total person years (y)	352.4	230.4	122.0	152.6	96.6	56.0
Mean unadjusted rate of events (events/1000 person-years)	1332	1519	993	843	915	722
Variance of unadjusted rate	648	646	649	646	661	620
Number of patients with more than 1 event	22	19	3	7	4	3
Number of events in patients with more than 1 event	46	40	6	14	8	6
Number of patients with at least one event	Xx	Xx	Xx	Xx	Xx	Xx
Incidence rate (95 % CI)	994.08 (912.02 - 1083.53)	1225.03 (1115.13 - 1345.76)	801.29 (695.41 - 923.29)	616.35 (527.97 - 719.52)	725.40 (600.62 - 876.09)	555.75 (432.23 - 714.58)
Standard Error of Mean	43.70	58.75	57.94	48.67	69.86	71.28
Scale - one value for each model	0.7701	0.7995	0.7140			