glomerular filtration rate clearance were significant risk factors for hyponatraemia in both sexes.

Ferring Pharmceuticals is currently developing FE 201836, another synthetic analogue of AVP and a potent and highly selective short-acting vasopressin-2 (V_2)-receptor agonist with an antidiuretic action profile suitable for treating nocturia due to NP in adults. FE 201836 exerts its antidiuretic effect by increasing the water permeability of the luminal membrane of the renal cortical and medullary collecting ducts, and thereby reducing free water excretion.

Hyponatraemia may develop over time if excessive drinking occurs during the period of antidiuretic drug effect. Therefore, the ideal V_2-receptor agonist should provide an antidiuretic duration of action not exceeding 6-8 hours i.e., corresponding to the night-time sleep period when drinking does not occur or is limited to a minimum (to satisfy thirst). The oral half-life should be shorter than that of desmopressin and the key route of metabolism non-renal, since the clinical promise of a short-acting V_2-receptor agonist is based on an improved safety profile without a prolonged duration of action leading to hyponatraemia. A shorter and more predictable duration of antidiuretic action would minimise the risk of hyponatraemia and may reduce the need for serum sodium monitoring.

In the present clinical trial, 6 doses of FE 201836 (50-500 µg) will be evaluated for estimation of the dose-response curve, where the response is the change in the number of nocturnal voids. The choice of FE 201836 doses is based on the data regarding the antidiuretic effect of FE 201836 in healthy subjects and by the antidiuretic effects of desmopressin in healthy subjects and in patients with NP.

In phase 1 trial 000195 in young healthy men and women oral doses of FE 201836 up to 4800 µg (i.e., 9.6 times higher than the suggested maximum dose in the present phase 2 trial) were administered and found to be safe and well tolerated. The exposure after intravenous infusion of 0.5 µg FE 201836, comparable to the exposure after an oral dose of approximately 900 µg FE 201836, resulted in approximately 8 hours of antidiuretic effect.

The present trial is powered for detecting differences in treatment effects between FE 201836 and placebo. Desmopressin is included as benchmark treatment. There is no prospectively planned power for conclusive inference with regards to differences between desmopressin and placebo (or FE 201836).

In order to select trial subjects with nocturia primarily due to the underlying condition of NP driven with increased Free Water Clearance (FWC), who will benefit the most from treatment with an antidiuretic agent, a 1-week active run-in period followed by a 1-week washout period (referred to as the 'enrichment period') will be applied to ensure that drug-responders (defined as a reduction of nocturnal diuresis [mL/min]of 20% or more) are identified. The ≥20% decrease in the nocturnal diuresis rate has been established as a relevant marker of antidiurectic responsiveness in previous nocturia trials with an active run-in. The majority of fluid output occurs via the urine, approximately 1,500 mL/day, therefore there is no evidence in adult nocturia patients that the

IUD	Intrauterine Device
IUS	Intrauterine System
KM	Kaplan-Meier
LAM	Lactational Amenorrhoea Method
LUTS	Lower Urinary Tract Symptoms
MED	Minimum Effective Dose
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not At Random
NLM	National Library of Medicine
NP	Nocturnal Polyuria
NPi	Nocturnal Polyuria index
NYHA	New York Heart Association
NI Diary	Nocturia Impact Diary©
NUV	Nocturnal Urine Volume
OAB	Overactive Bladder
ODT	Orally Disintegrating Tablet
OSA	Obstructive Sleep Apnoea
PAP	Psychometric Analysis Plan
PD	Pharmacodynamic
PGI-I	Patient Global Impression of Improvement
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PP	Per Protocol
PRO	Patient Reported Outcome
RAAS	Renin-Angiotensin-Aldosterone System
REB	Research Ethics Board
RLS	Restless Legs Syndrome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIADH	Syndrome of Inappropriate Antidiuretic Hormone
SOC	System Organ Class
SRC	Safety Review Committee
SSRI	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction

- Change from baseline in NI Diary Overall Impact Score at Weeks 1, 4, 8 and 12 and during 12 weeks of treatment.
- Patient Global Impression of Improvement (PGI-I) urinary symptoms scores at Weeks 1, 4, 8 and 12.
- Change from baseline in Patient Global Impression of Severity (PGI-S) scores at Weeks 1, 4, 8 and 12.
- Change from baseline in Bother as measured by the Hsu 5-point Likert Bother scale (Hsu, 2015) at Weeks 1, 4, 8 and 12.
- Change from baseline in Insomnia Severity Index (ISI) at Weeks 4, 8 and 12.
- Change from baseline in FUSP at 1, 4, 8 and 12 weeks of treatment and during 12 weeks.
- Change from baseline in nocturnal diuresis rate (hourly) profiles at Week 1 and Week 12.
- Change from baseline in Nocturnal Urine Volume (NUV) at Week 1 and Week 12.

Safety Endpoints

- Incidence and severity of adverse events.
- Incidence of hyponatraemia as measured by serum sodium level throughout the trial.
- Change from baseline in mean 24-hour urine volume at Week 1 and Week 12.
- Clinically significant changes in vital signs and laboratory values.

Exploratory Endpoints

- Responder rates defined as 33%, 60%, 70%, 80%, 90% and 100% reduction from baseline in number of nocturnal voids at Weeks 1, 4, 8 and 12.
- Responder rates defined as 1, 2, and 3 voids reduction from baseline in number of nocturnal voids at Weeks 1, 4, 8 and 12.
- The correlation of copeptin levels to NPi at Visit 2.
- Change from baseline in copeptin levels at Week 12.
- Change from baseline in total sleep time per night at Weeks 1, 4, 8 and 12 and during 12 weeks of treatment.
- Correlation between change from baseline in total sleep time and FUSP at Weeks 1, 4, 8 and 12.
- Change from baseline in NPi at Week 1 and Week 12.

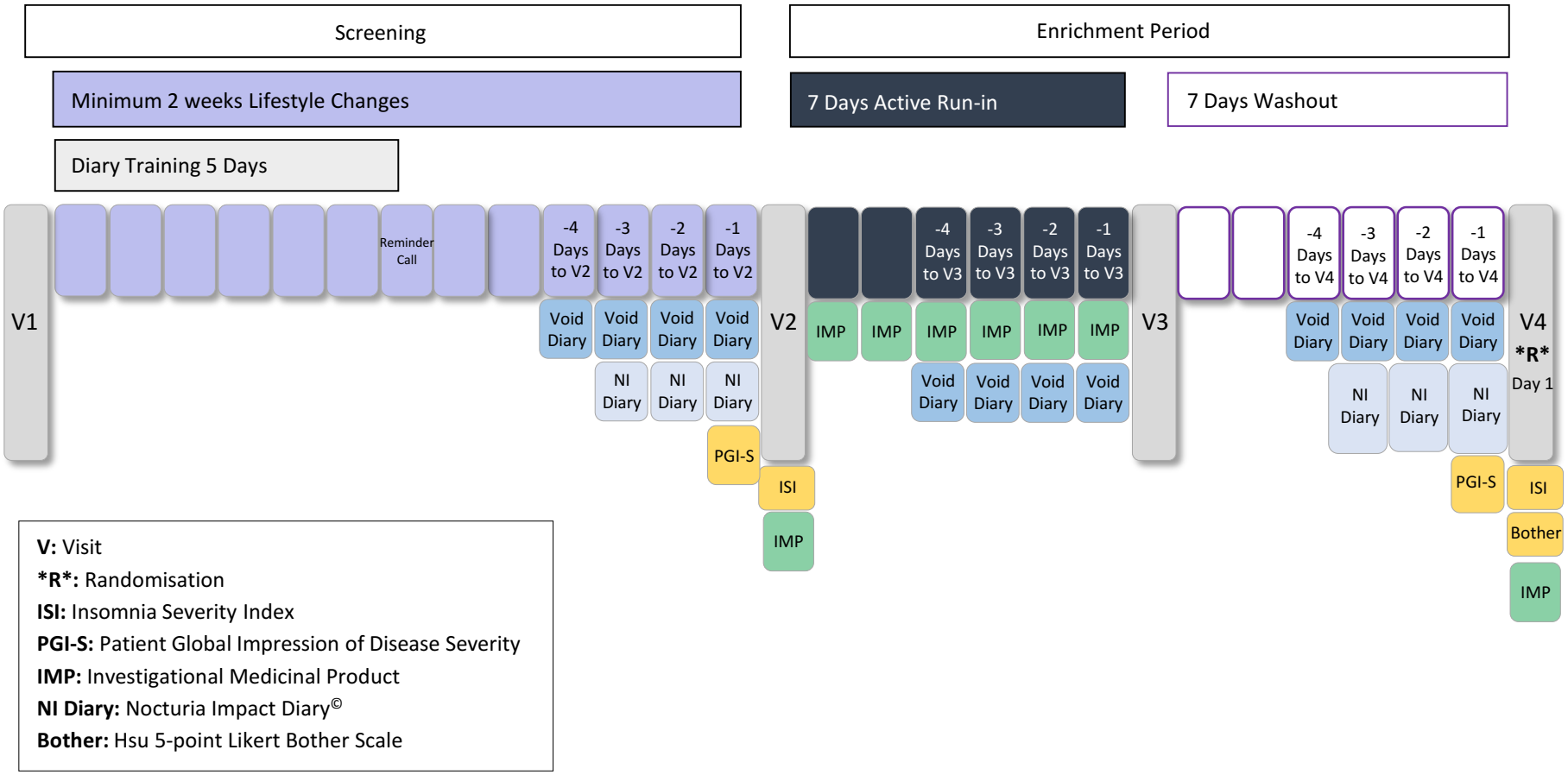


Figure 3-2 e-Diary Assessments and Questionnaires to be Completed by the Subject Prior to Randomisation

Safety, including serum sodium levels (Section 7.1.3.1), adverse events and clinically significant changes in vital signs and laboratory values will be monitored throughout the trial and reviewed on an ongoing basis by a Safety Review Committee (SRC) (Section 3.4).

Furthermore, the risk for subjects developing hyponatraemia will be mitigated by a serum sodium monitoring plan (Section 7.1.3.1), including a 1-week active run-in to identify subjects at increased risk for developing acute hyponatraemia prior to randomisation. If the incidence of serum sodium levels <130 mmol/L is statistically significantly >10% during the active run-in, the Data Monitoring Committee (DMC) established for the trial (Section 3.4) will be notified and further action will be discussed, e.g., the DMC may recommend that the highest dose of FE 201836 may be replaced by a lower dose. The trial is designed so the dose may be lowered from 500 µg to 350 µg if recommended by the DMC, as described in Section 9.11.1.

3.1.3 Trial Schedule

The first trial visit (Visit 1, screening) for the first subject is expected in Q3 2017 and the last trial visit for the last subject is expected in Q3 2019. The total duration of the trial (for a subject) is expected to be approximately 18 weeks (including the exit interview).

Trial completion is defined as when the last subject has completed the last visit in the randomised trial period (Visit 8).

3.2 Planned Number of Trial Sites and Subjects

The trial will be conducted at approximately 70 sites in Europe and North America. A maximum of 300 subjects will be included (Section 9.1).

3.3 Interim Analyses

Interim analyses will be performed by an internal DMC established for the trial.

The first interim analysis will be conducted after an initial 125 subjects have been randomised in a 2:2:1 ratio to placebo, 500 µg FE 201836 or desmopressin.

After the first 125 randomised subjects, the allocation ratio is 2:7:1 for placebo, active treatment and desmopressin, respectively. Subsequent interim analyses will be performed every 8 weeks, where the randomisation allocation probabilities to FE 201836 doses will be adjusted.

The interim analyses are detailed in Section 9.11.

3.4 Safety Review and Data Monitoring Committees

Trial data will be reviewed on an ongoing basis by the sponsor SRC.

In addition, an internal DMC will be established for the trial. The main purpose of the DMC is to perform pre-planned interim analyses (Section 3.3) and make recommendations based on review of the efficacy and safety data. An additional purpose of the DMC is to address any potential safety concerns raised by the SRC. The responsibilities and the composition of the DMC are provided in a separate charter document.

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

The present clinical trial includes a 2-week period of lifestyle changes. Lifestyle changes (e.g., limiting fluid intake) are recommended as an initial treatment in most clinical guidelines, e.g., the updated American Urology Association (AUA) guideline on the management of BPH (McVary, 2011), despite the relative paucity of supporting data (Weiss, 2013). Excluding pelvic floor exercises for bladder-related Lower Urinary Tract Symptoms (LUTS), which are not part of the present trial, there seems to be no evidence that prolonged lifestyle changes, versus the proposed 2 weeks in the present trial, will result in additional benefit on NP related to excessive nocturnal fluid intake. From a practical point of view, the total of 4 weeks during the pre-randomisation period in the present trial is considered adequate for subject compliance.

In order to select subjects with nocturia primarily due to the underlying condition of NP driven with increased Free Water Clearance (FWC), who will benefit the most from treatment with an antidiuretic agent, a 1-week active run-in period followed by a 1-week washout period will be applied to ensure that drug-responders (defined as subjects with a reduction of nocturnal diuresis rate [mL/min] of 20% or more) are identified.

The ≥20% decrease in the nocturnal diuresis rate has been established as a relevant marker of antidiurectic responsivenes in previous nocturia trials with an active run-in (Lose, 2003; Mattiasson, 2002). The NUV is defined as the total urine volume from 5 minutes after bedtime with the intention to sleep until the first void within 30 minutes of rising in the morning. Total time in bed is a proxy for the time the subject is in nocturnal diuresis. The nocturnal diuresis rate is calculated from the mean of 3 days NUV and total time in bed:

$$Nocturnal\ diuresis\ rate\ (mL/min) = \frac{\text{NUV (mL)}}{\text{Total Time in Bed (min)}}$$

The majority of fluid output occurs via the urine, approximately 1500 mL/day, therefore threre is no evidence in adult nocturia subjects that the relative change over the time in nocturnal diuresis rate (mL/min normalised to time in bed) should be adjusted for body weight and or/body surface area which are both assumed to be constant over a short period of 1 week only. An analysis of individual nocturia subject data found that reducing NUV and increasing the duration of antidiuretic action of a V_2-receptor agonist (desmopressin) was a significant predictor for subsequent decrease from baseline in the number of nocturnal voids (Yamaguchi, 2013).

The underlying pathophysiologic mechanism of NP can be driven by either increased FWC, which based on mode of action will be responsive to antidiuretic treatment, or by increased sodium clearance, which differs substantially in mode of action and is governed by Atrial Natriuretic Peptide (ANP) which is directly and indirectly influenced by the Renin-Angiotensin-Aldosterone System (RAAS).

The aim of the active run-in is (after excluding all other medical causes of NP) to identify subjects with increased FWC, which is responsive to V_2-receptor agonism. In addition, safety will be assessed in this period with special emphasis on hyponatraemia.

Treatment group allocation will be determined by central randomisation to eliminate selection bias and ensure that any difference in treatment groups at baseline is a result of random chance. Following randomisation at Visit 4, a double-blind design has been chosen to minimise both investigator and subject ascertainment bias. In order to keep the treatment blinded each subject will receive two medications throughout the trial; an oral solution and an ODT, i.e., a double-dummy design will be applied because desmopressin is available in an ODT formulation and FE 201836 is an oral solution. The blinding is further described in Section 5.5.

Interim analyses will be conducted throughout the trial in order to investigate the efficacy of FE 201836 and to reassess the randomisation probabilities for each dose of FE 201836 based on observed responses at the respective interim locks. In addition, serum sodium will be monitored during the active run-in in order to identify subjects at increased risk of developing acute hyponatraemia. The interim analyses are further described in Section 3.3 and Section 9.11.

3.5.2 Selection of Endpoints

The change in mean number of nocturnal voids has become a standard primary clinical trial endpoint in nocturia trials since the first overseas trials (with desmopressin) in early 2000 (Lose, 2003; Mattiasson, 2002; van Kerrebroeck, 2007). It is therefore reasonable and appropriate to use reduction in number of nocturnal voids from baseline as the primary endpoint in this trial.

Nocturia is one of the primary causes of sleep disturbance and has been shown to impair functioning, quality of life, health and productivity, with those experiencing 2 or more voids per night reporting significant bother (Ancoli-Israel, 2011). Awakening during the first 3-4 hours of the night during the deep and slow-wave restorative sleep is more likely to contribute to daytime fatigue (Chartier-Kastler, 2006). The clinically relevant benefit (for the subject) of desmopressin treatment may be demonstrated further by measuring the time to first awakening to void (FUSP), which reduces the time spent in slow wave (deep) sleep (Bliwise, 2015). Therefore it is reasonable to include FUSP as an endpoint in the present trial. To further evaluate the clinical benefit of FE 201836 endpoints relating to percentage of nights with at most one nocturnal void or with complete response are included for analysis.

The significant impact of nocturia and its treatment on subjects' quality of life and daily lives will be documented by the use of an e-Diary which contains a 3-day voiding diary, NI Diary and PRO questionnaires. Voiding diaries are standard tools used within the urology area (Holm-Larsen, 2009) and are among the best possible means of obtaining objective data on subjective symptoms (Abrams, 1983). A voiding diary therefore represents a self-monitoring daily record of the individual's voiding behaviour. The ICS recommends inclusion of voiding diaries in clinical assessment of subjects with LUTS (Abrams, 2002). The subjects will be asked to complete voiding diaries over 3 consecutive 24-hour periods just prior to scheduled visits throughout the trial. Three-day voiding diaries have been shown to be as effective as 7-day diaries with the potential for better accuracy (Dmochowski, 2005).

The NI Diary, is a 12-item PRO measure assessing the impact burden associated with nocturia (Holm-Larsen, 2014). The NI Diary has been developed and psychometrically evaluated in patients with nocturia, in line with published International Society for Quality of Life Research (ISOQOL)

and International Society for Pharmacoeconomic and Outcomes Research (ISPOR) guidance (Patrick, 2011; Reeve, 2013), as well as the Food and Drug Administration (FDA) Guidance for Industry, Patient-Reported Outcome Measures, 2009 (FDA, 2009).

The PGI-S and PGI-I questionnaires, developed for use in populations with urinary tract conditions (Viktrup, 2012; Yalcin, 2003), are included to support anchor-based analysis of the NI Diary, as described in Section 10.3.1.

To further assess the change in subjective bothersomeness of nocturia, trial participants will be asked, "How much has this frequency of night-time urination bothered you?" with response options including "not at all," "slightly," "moderately," "quite a bit," and "extremely." This 5 point Likert scale has previously been used in a large epidemiological study (Hsu, 2015).

The ISI is a PRO instrument to quantify the subject's perception of his/her insomnia severity, it is included as a measure of sleep quality. The ISI targets the subjective symptoms and consequences of insomnia as well as the degree of concern or distress caused by those difficulties (Bastien, 2001).

Table 6-1 Trial Flow Chart

Assessment	Screening/ Lifestyle Changes		Active Run-in Period		Washout Period	Randomised Trial Period				
Visit (V)	V1	Reminder	V2	Telephone Follow-up	V3	V4 [L]	V5	V6	V7	V8 [O]
Week							1	4	8	12
Day/Visit window	Sl		-14	-10±1 [m]	-7 [n]	1	8±2	28±3	56±3	84±7
Informed consent	X									
Inclusion and exclusion criteria	X		X		X	X				
Lifestyle Changes [a]	X	X	X	X	X	X	X	X	X	
Randomisation						X				
Dispense e-Diary	X									
e-Diary Training	X	[b]								
e-Diary Compliance			X		X	X	X	X	X	X
Dispense IMP			X			X	X	X	X	
Accountability of IMP					X		X	X	X	X
Demographics	X									
Medical history	X									
Physical examination	X					X				X
Body weight	X		X		X	X	X	X	X	X
Height	X									
Vital Signs [c]	X		X		X	X	X	X	X	X
Electrocardiogram (ECG)	X									X
Pregnancy test - serum [d]	X					X				X
Pregnancy test - urine [d]	X									
Clinical chemistry, haematology, urinalysis	X					X	X	X	X	X
Coagulation factors	X					X		X		X
Copeptin			X			X				X
OSA assessment [e]	X									
Serum sodium [p]	X [j]				X [k, n]		X	X	X	X
Voiding Diary [f]			X		X	X	X	X	X	X
NI Diary [f]			X			X	X	X	X	X
PGI-S [g]			X			X	X	X	X	X
PGI-I [g]							X	X	X	X
ISI [h]			X			X		X	X	X
Bother [h]						X	X	X	X	X
Exit Interview [i]										X
Adverse events			X	X	X	X	X	X	X	X
Concomitant medication	X		X		X	X	X	X	X	X

a. Subjects will be reminded about lifestyle changes throughout the trial.
b. Original footnote omitted as per Clinical Trial Protocol Amendment 03 (applicable for all trial sites).
c. Vital signs (blood pressure and heart rate) measured after resting for 5 minutes in a sitting position.
d. Applicable to all pre- and perimenopausal female subjects.
e. Original footnote omitted as per Clinical Trial Protocol Amendment 03 (applicable for all trial sites).
f Completed by the subjects at home over 3 consecutive days just prior to scheduled visits.
g. Completed at home 1 day prior to scheduled visits.
h. Completed at the site visit before any consultation with the trial site personnel takes place.
i. A sample of subjects (at trial sites in the USA) who completed the trial will be invited to participate, by telephone, in an exit interview within 14 days of attending Visit 8.
j. If serum sodium is <135mmol/L the test should be repeated within 7 days, if the second result is <135mmol/L the subject must be discontinued from the trial as a 'screening failure'. If more than 21 days elapse between the serum sodium measurement at Visit 1 and Visit 2, the serum sodium measurement must be re-tested, with results available prior to Visit 2.
k. If serum sodium is <130mmol/L the investigator must immediately contact the subject and schedule visits for further evaluation , if the serum sodium is <130mmol/L (results confirmed within 7 days) the subject will not be randomised to the trial and must be discontinued from the trial as a 'screening failure'.
l. Baseline efficacy.
m. During the 1 week active run in period, 4 days (±1 day) after the planned start of IMP treatment, the subject will be telephoned to follow up on safety.
n. If the subject cannot attend Visit 3 as planned, arrangements must be made to test the serum sodium level at Day 6-8 from the IMP start date.
o. The end-of-trial visit (Visit 8) should be performed if the subject discontinues the trial prior to Visit 8.
p. Sample to be taken preferably in the morning.

should be described (including the reason for the visit) and documented in the medical/source record, and in the eCRF.

Table 7-1 Timing of Voiding Diary Assessments

Voiding Diary Assessment	3 Consecutive Days Prior to Visit(s)
Time of Going to Bed with the Intention to Sleep	2, 3, 4, 5, 6, 7, 8
Time of Awakening in the Morning	2, 3, 4, 5, 6, 7, 8
Assessment of Urgency and Incontinence Episodes	2
Number and Timing of Nocturnal Voids	6, 7
Number and Timing of Voids during 24-hours	2, 3, 4, 5, 8
Nocturnal Urine Volume	3*
24-hour Urine Volume	2, 4, 5, 8

* Includes collection of total urine volume within 30 minutes of rising (in the morning)

Effort should be made to ensure that the subject fills out the voiding diary (in the e-Diary) on the same weekdays throughout the trial for consistency, e.g., if the first voiding diary (in the e-Diary) is started on a Monday, the subsequent e-Diary should also be started on a Monday (Table 7-2). During the night (the sleep period) before the visit no measurements will be recorded.

Table 7-2 Example of Voiding Diary Completion When Visit Planned for Friday

	Monday Day-4	**Tuesday** Day -3	**Wednesday** Day-2	**Thursday** Day-1	**Friday Visit Day**	**Saturday**	**Sunday**
Morning		X	X	X			
Afternoon/ Evening		X	X	Finish voiding diary (in e-Diary) X			
Night	Start voiding diary (in e-Diary) X	X	X				

During the screening period, each subject must complete the 3-day voiding diary to document the severity of nocturia and to confirm the eligibility for the active run-in period. The voiding diary should be completed over 3 consecutive 24-hour periods just prior to Visit 2.

During the 1-week active run-in period, each subject must complete a 3-day voiding diary to document treatment response of ≥20% decrease in the nocturnal diuresis (mL/min) that was recorded at Visit 2 and confirm the eligibility. The voiding diary should be completed over 3 consecutive 24-hour periods just prior to Visit 3.

commonly reported symptom by individuals and causes a great amount of interferences with daily life. Sleepiness has also been linked to increased risks for accidents, such as falling asleep while driving or work-related accidents (Asplund, 2005; Ancoli-Israel, 2011).

Nocturia is characterised by shortening the FUSP. The first sleep period is of high importance due to that deepest stages of sleep (most restorative sleep) typically occur within the first few hours of the sleeping and once these stages are interrupted by wakening (e.g., to void) patients are not able to make up for this during the rest of the night (Bliwise, 2015). FUSP will be a secondary endpoint in the trial.

Sleep quality will be measured through the ISI, which is an instrument to quantify the subject's perception of his/her insomnia severity. The ISI targets the subjective symptoms and consequences of insomnia as well as the degree of concern or distress caused by those difficulties (Bastien, 2001).

The ISI comprises of four `sleep-related' items and three `wake-related' items assessing the severity of sleep-onset and sleep maintenance difficulties (both nocturnal and early morning awakenings), satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem and degree of distress or concern caused by the sleep problem. Each item is rated on a 0-4 scale and the total score ranges from 0 to 28. A higher score suggests more severe insomnia.

The self-administered ISI questionnaire will be completed at the trial site by the subject before active run-in period (Visit 2), at the randomisation visit (Visit 4), after 4 weeks (Visit 6), after 8 weeks (Visit 7) and at the last trial visit after 12 weeks of treatment (Visit 8) as illustrated in Figure 3-2 and Figure 3-3. Since the ISI has a two-week recall, a reminder to think back two weeks will appear on the screen upon start of completion, in order to improve on quality of the information captured. The ISI will be completed at Visit 2 in order to compare insomnia severity to other diseases presenting with insomnia, as recorded by the ISI. The ISI completed at the remaining visits (Visits 4, 6, 7 and 8) will be used to measure treatment effect.

7.1.1.3.3 Bother

Patient bother is a broad concept covering aspects such as impact on sleep, daily life, social life, mental health, fatigue, etc. (Tikkinen, 2010). It has been shown that most nocturia patients are not very bothered by one nightly void, but that there is clearly a bother threshold at two voids or more. Moreover, comparing two adjacent voiding categories at a time, the increase was statistically significant with each increment in number of nightly voids. To further assess the change in subjective bothersomeness of nocturia, trial participants will be asked, “How much has this frequency of night-time urination bothered you?” with response options including “not at all,” “slightly,” “moderately,” “quite a bit,” and “extremely.” This 5-point Likert scale has previously been used in a large epidemiological study (Hsu, 2015).

The Hsu 5-point Likert Bother Scale will be completed by the subject at the trial site at randomisation (Visit 4), after 1 week (Visit 5), after 4 weeks (Visit 6), after 8 weeks (Visit 7) and at the last trial visit after 12 weeks of treatment (Visit 8), as illustrated in Figure 3-2 and Figure 3-3.

7.1.3.1 Serum Sodium

Serum sodium levels will be monitored throughout the trial as hyponatraemia is a potentially serious adverse drug reaction (ADR) associated with desmopressin treatment and may potentially be associated with FE 201836 treatment.

A central laboratory will be used. However, a local laboratory may be used in addition to the central laboratory if a quick turn-around time of the result is needed. In such case a sample must also be sent to the central laboratory. Evaluation of the laboratory-based eligibility criteria will be determined by the central laboratory results. All serum sodium values must be reviewed as soon as possible after the results are available. Any unexpected low serum sodium value must be re-tested. Any significant changes in serum sodium, judged by the investigator as clinically significant must be reported as adverse events, as described in Section 8.2.

Blood samples for analysis of serum sodium will be collected, preferably in the morning, at Visits 1, 3, 5, 6, 7 and 8, as presented in Table 6-1. The risk for subjects developing hyponatraemia during the trial period will be mitigated as follows (serum monitoring plan):

Screening (Visit 1)

All subjects must have normal serum sodium (≥135 mmol/L) at screening (Visit 1). If the serum sodium value is <135 mmol/L (re-tested and confirmed, with results available within 7 days) the subject must be discontinued from the trial as a 'screening failure'.

Active Run-in Period

During the 1-week active run-in period, 4 days (±1 day) after the planned start of IMP treatment, the subject will be telephoned to follow-up on safety.

Visit 3

At Visit 3 (after the active run-in), if the serum sodium value is <130 mmol/L the investigator must immediately contact the subject and schedule visits for further evaluation. If the serum sodium value is <130 mmol/L (re-tested and confirmed, with results available within 7 days) the subject will not be randomised to the trial and must be discontinued from the trial as a 'screening failure'. The subject will be followed (by the investigator) for safety until the serum sodium level is stable and not clinically significant, preferably until at least ≥135 mmol/L.

If the subject cannot attend Visit 3 as planned, arrangements must be made to test the serum sodium level at Day 6-8 from the IMP start date to ensure the serum sodium level is measured while the subject is taking IMP.

12-week Randomised Treatment Period

During the 12 weeks randomised treatment period, any unexpected low serum sodium value (<135 mmol/L or a drop in serum sodium level >10 mmol/L) must be re-tested with at least 2 additional consecutive tests to identify the nadir and duration of the hyponatraemic episode. The serum sodium level should be re-tested within 5 (±2 days) since the previous test. The subject will be followed (by the investigator) for safety until the serum sodium level is stable and not clinically significant, preferably until at least ≥135 mmol/L.

Body weight (without overcoat and shoes) will be measured at all visits. The same scale should preferably be used on the subject during the course of the trial for consistency in readings.

If the subject has gained more than 2 kilograms between trial visits, the serum sodium level must be measured, as described in Section 7.1.3.1.

7.2.5 Physical Examination

Physical examinations will be performed at Visits 1, 4 and 8 by the investigator or a delegated sub-investigator (MD, Medical Doctor; DO, Doctor of Osteopathic Medicine; PA, Physician Assistant; NP, Nurse Practitioner) and must not be delegated to any other trial site personnel. The same individual should preferably perform the physical examinations for a subject for consistency in evaluation.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, urological and neurological systems. Any abnormal, clinically significant changes should be reported as adverse events.

7.2.6 Pregnancy Test

A serum pregnancy test will be performed in all pre- and peri-menopausal female subjects at screening (Visit 1), Visit 4 and at the end-of-trial visit (Visit 8). A urine pregnancy test will also be performed at screening (Visit 1).

Female subjects of childbearing potential must have documentation of an acceptable effective method of contraception, as described in Section 4.3.4. Amenorrhea of >12 months duration based on the reported date of the last menstrual period is sufficient documentation of post-menopausal status and does not require a pregnancy test.

7.2.7 Electrocardiogram

A 12-lead ECG will be performed by the investigator or appropriate designee at the screening visit (Visit 1) and at the end-of-trial visit (Visit 8). The ECG should be taken after resting for 5 minutes. The ECG print-out should be reviewed, signed and dated by the investigator. Any abnormal, clinically significant changes should be reported as adverse events.

7.3 Handling of Biological Samples

A trial-specific laboratory manual will be provided to the participating sites, describing in detail how to handle, store and transport the biological samples in this trial. All biological samples will be analysed at central laboratories and will be destroyed after the results are available. For all biological samples collected in the trial, analyses beyond those described in the protocol can only be performed after obtaining the required approvals. The processes related to handling biological samples will be described in the informed consent documents and data protection legislation including local legislation will be adhered to.

In addition to the central laboratory, a local laboratory may be used for analysis of serum sodium if a quick turn-around time of the result is needed (Section 7.1.3.1).

- Action taken to IMP
- Other action taken
- Date and time of outcome (time can be omitted, if applicable)
- Outcome
- Seriousness.

Each of the items in the Adverse Event Log is described in detail in the following sections.

Adverse Event
Adverse events should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.

If a subject suffers from the same adverse event more than once and the subject recovers in between the events, the adverse events should be recorded separately. If an adverse event changes in intensity, a worst-case approach should be used when recording the event, i.e. the highest intensity and the longest duration of the event.[a]

Note the following: A procedure is not an adverse event; the reason for conducting the procedure is. Hospitalisation is not an adverse event; the reason for hospitalisation is. Death is not an adverse event, but the cause of death is (an exception is sudden death of unknown cause, which is an adverse event).

Date and Time of Onset
The date of onset is the date when the first sign(s) or symptom(s) were first noted. If the adverse event is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken or the examination was performed.

Intensity
The intensity of an adverse event must be classified using the following 3-point scale:

Mild: Awareness of signs or symptoms, but no disruption of usual activity.

Moderate: Event sufficient to affect usual activity (disturbing).

Severe: Inability to work or perform usual activities (unacceptable).

[a] Exception: if an adverse event with onset before the first IMP administration (i.e., a pre-treatment adverse event) worsens in intensity, this must be recorded as two separate events. The initial adverse event should be recorded with outcome "not recovered" and the date and time of outcome is when the intensity changed. The second adverse event should be recorded with date and time of onset when the intensity changed.

8.5 Serious Adverse Events

8.5.1 Serious Adverse Event Definition

Table 8-1 Serious Adverse Events during the Trial

An event is defined a serious adverse event if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within 4 weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a subject enrolled in a trial is *per se* not an event, but an outcome.
is **life-threatening**	The term life-threatening refers to an adverse event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient **hospitalisation** or prolongation of existing hospitalisation	The term hospitalisation means that the subject was admitted to hospital or that existing hospitalisation was extended as a result of an event. Hospitalisation describes a period of at least 24 hours. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalisation. However, medical judgement must always be exercised and when in doubt the case should be considered serious (i.e., if case fulfils the criterion for a medically important event). Hospitalisations for administrative or social purposes do not constitute an SAE. Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
results in persistent or significant **disability/incapacity**	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgement by the investigator.
is a **congenital anomaly/birth defect**	Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the IMP.
is an **important medical event**	Important medical events are events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include adverse events that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgement should be exercised in deciding whether events qualify as medically important. Important medical events include any suspected transmission of an infectious agent via a medicinal product. Any organism virus or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a subject exposed to a medicinal product.

8.5.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

An SAE must be reported **immediately** to Ferring Global Pharmacovigilance as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

The investigator is responsible for submitting the completed SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

The SAE Report Form is included in the eCRF system and must be completed. In case the eCRF cannot be accessed and hence the SAE Report Form cannot be filled in within the eCRF system, a paper SAE Report Form available in the investigator's file should be used and sent to Ferring Global Pharmacovigilance using the contact details below:

Global Pharmacovigilance, Ferring Pharmaceuticals A/S

E-mail: [redacted]

Fax: [redacted]

eCRF information regarding demographics, adverse events, medical history and concomitant medication is **mandatory** for initial reports and for follow-up reports if any changes have been made since the initial report.

Additional information relevant to the SAE such as hospital records, results from investigations, e.g. laboratory parameters (that are not already uploaded in the eCRF), invasive procedures, scans and x-rays and autopsy results can be faxed or scanned and e-mailed to Ferring Global Pharmacovigilance using the contact details in the section above. In any case this information must be supplied by the investigator upon request from the sponsor. On any copies provided, such details such as subject's name, address and hospital ID number should be concealed and instead subject number should be provided.

The investigator will supply the sponsor and the IEC/IRB/REB with any additional requested information such as results of post-mortem examinations and hospital records.

Expedited Reporting by the Sponsor

The sponsor will report all adverse events that are **serious, unexpected and with a reasonable possible causality to the IMP** (referred to as suspected unexpected serious adverse reactions [SUSARs]) as judged by either the investigator or the sponsor to the relevant parties (i.e., investigators, IECs/IRBs/REBs and regulatory authorities) within the stipulated timelines. The expectedness is assessed by the sponsor according to the current Investigator's Brochure for FE 201836. Unblinded SAEs will be assessed using the current relevant reference safety information, which for FE 201836 is in the Investigator's Brochure and for desmopressin in the Decentralised Procedure NOCDURNA Summary of Product Characteristics.

SAEs will be considered reportable regardless of whether or not the IMP was used in accordance with the provisions in the protocol and the applicable reference safety information document.

8.6 Follow-up of Adverse Events and Serious Adverse Events

8.6.1 Follow-up of Adverse Events with Onset during the Trial

During the trial, the investigator must follow-up on each adverse event until it is resolved or until the medical condition of the subject is stable.

After the subject's last visit, the investigator must follow-up on any adverse event classified as serious or considered to have a reasonable possible causality to the IMP until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to the sponsor. If the event is a chronic condition, the investigator and the sponsor may agree that further follow-up is not required.

8.6.2 Collection of Serious Adverse Events with Onset after Last Visit in the Trial

If an investigator becomes aware of an SAE after the subject's last visit and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to the sponsor via the paper SAE Report Form, regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

The Global Biometrics Department at Ferring Pharmaceuticals A/S will be responsible for data management, the Statistical Analysis Plan (SAP) and the statistical analyses, production of tables, listings and figures. This section outlines the planned statistical analysis of the primary endpoint and the planned statistical analyses for the secondary endpoints. All analyses and further description of the statistical methodology for primary as well as secondary endpoints will be detailed in the SAP. The SAP will be available before the first interim analysis.

The analysis concerning the psychometric validation of the NI Diary is provided in a separate PAP.

9.1 Operating Characteristics

The operating characteristics and associated power are estimated for different dose-response scenarios by computer simulations using the Fixed and Adaptive Clinical Trial Simulator (FACTS) version 5.6. The five sigmoidal dose-response profiles that were used to simulate trial data are illustrated in Figure 9-1. Further details on the dose-response model and the associated primary analysis are given in Section 9.7.2 and Appendix 2.

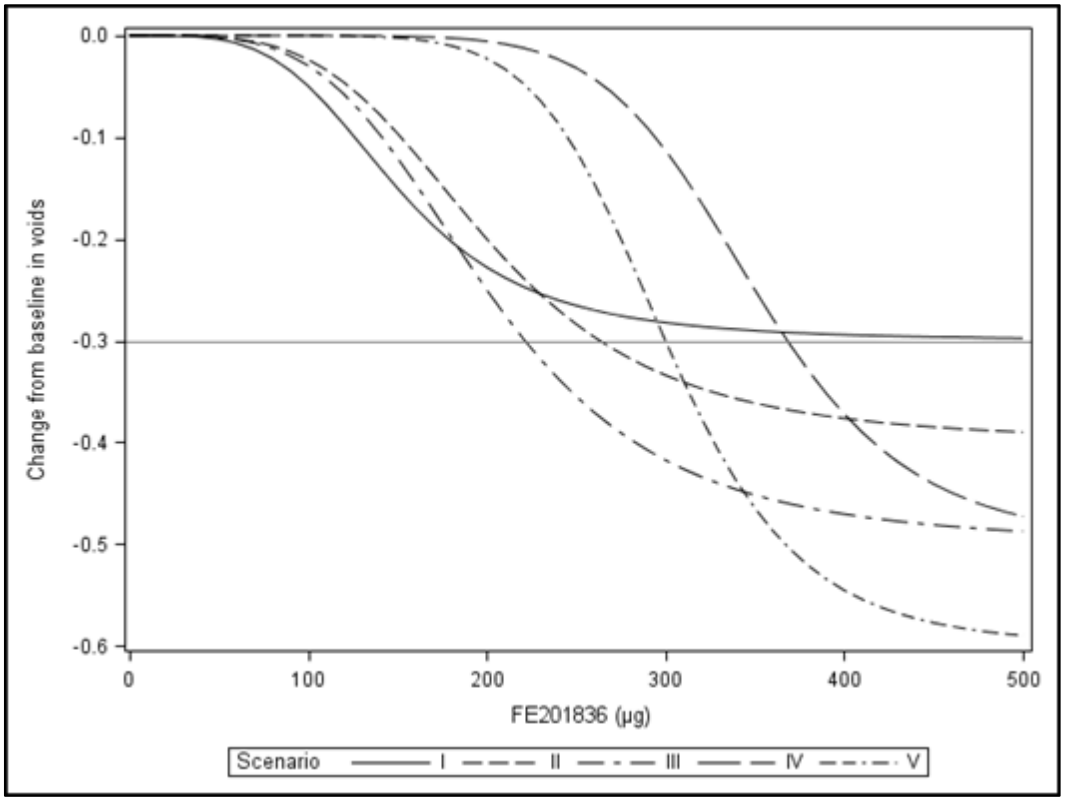


Figure 9-1 Dose-Response Scenarios

For endpoints obtained in the e-Diary prior to a visit, the 3-day e-Diary data will be averaged and interpreted as the observation of the endpoint in question.

If nothing else is stated the Bayesian dose-response analyses are conducted with respect to the time-averaged treatment effect. The posterior means estimates, 95% credibility interval of the estimates and posterior probabilities of quantities of interest will be reported.

Frequentist inferences will rely on the appropriate choice of model and report p-values corresponding to the statistical test of the hypothesis of "equal effect" against the alternative of "different effect". The level of significance is set at 5% (two-sided).

Treatment comparison refers to the pair-wise comparison between active doses and placebo. There are no planned adjustments for multiplicity when pair-wise testing any active dose of FE 201836 versus placebo. Desmopressin is included as a benchmark treatment only. None of the primary, secondary or explorative analyses will include desmopressin. Explorative benchmarking analyses are furher described in Section 9.8.

9.7.2 Primary Analysis

The objectives of the primary analysis are to establish Proof-of-Concept of FE 201836 and to estimate the dose-response profile of FE 201836. The dose-response is the average reduction from baseline in nocturnal voids during the randomised period. Proof-of-concept will be evaluated by the posterior probability that FE 201836 has superior efficacy as compared to placebo. Similarly, interim analysis futility criteria will be evaluated by pre-defined quantities of interest.

This section provides a brief background on the statistical Bayesian model that is utilised.

9.7.2.1 Statistical Dose-Response Model

Let $x_{t,i}$ denote the observed cross-sectional change from baseline in nocturnal voids (averaged across three consecutive nights) and let $y_{t,i}$ denote the time-averaged change from baseline for subject i up to time t:

$$y_{t,i} = \frac{\sum_{k=1}^{t} x_{k,i}}{t},\ t = 1,2,3,4,$$

where t denotes the nominal post-baseline time-point reflecting data observed at Weeks 1, 4, 8 and 12 (Visits 5, 6, 7 and 8, respectively). The final endpoint, $y_{4,i}$, is modelled as being an observation of $Y_{4,i} \sim N(\mu_{d,i}, \sigma^2)$ where the dose-response at dose d for subject i is adjusted for the number of baseline voids ($x_{0,i}$) and assumed to follow a sigmoidal model:

$$\mu_{d,i} = \beta x_{0,i} + \alpha_1 + \frac{(\alpha_2 - \alpha_1) d^{\alpha_4}}{d^{\alpha_4} + \alpha_3{}^{\alpha_4}} = \beta x_{0,i} + \mu_d,$$

9.7.3 Secondary and Explorative Analyses

The following main categories of inferential analyses will be performed for the secondary endpoints:

- Bayesian estimation of the Sigmoidal dose-response curve will follow the analysis described in Section 9.7.2.3. Prior distributions for primary analysis are specified in Appendix 2, while prior distributions for secondary analyses will be specified in the SAP. The dose-response model for the 50% responder rates will also be further detailed in the SAP.
- Continuous treatment effects at a certain visit will be analysed using SAS PROC MIXED assuming a repeated measures ANCOVA. (A non-parametric dose-response curve is assumed.) The changes from baseline per visit will be regressed upon the baseline observation as covariate and treatment, visit and treatment-by-visit interaction as factors. An unstructured covariance structure will be used for the random subject effect. Least square mean estimates of the changes from baseline and the treatment contrasts (with associated 95% confidence intervals) versus placebo will be tabulated and the changes from baseline will be graphically illustrated. Should only one post-baseline visit be obtained for an endpoint, an ANCOVA will be performed without the visit and treatment-by-visit interaction terms.
- Correlation between endpoints will be reported using Pearson correlation coefficients and partial correlation where applicable.
- Binary endpoints such as "responder status" at a certain visit will be analysed using SAS PROC GENMOD with the logit as link function for the responder probability. An unstructured covariance matrix will be assumed for the repeated responder status which will be adjusted for baseline value as covariate and treatment, visit and treatment-by-visit interaction as factors. (Associated with e.g., responder analysis in terms of reduction in number of voids, cumulative distritubtion function plots of percentage change from baseline by treatment may be produced.)

Table 9-4 presents the planned analyses.

Illustration of the therapeutic window is described separately in Section 9.7.3.1 and safety related endpoints are further described in Section 9.10.

Explorative gender analyses are planned for all endpoints. For these the following are noted:

- Estimates of the gender specific dose-response during 12 weeks of treatment will follow the analysis described in Section 9.7.2.3 by conducting separate analysis for each gender. Possible differences between the gender specific models will be investigated.
- Regression models will include gender and gender-by-treatment as factors. (Possible differences between the treatment effects on gender will be evaluated by the interaction term gender-by-treatment.)

Correlation analyses will be done separately for each gender.

Table 9-6 Definition of Hyponatraemic Episodes by Serum Sodium Range during the Randomised Treatment Period

Serum Sodium Range (mmol/L)	Number of Serum Sodium Observations
≥135	Not applicable (normal serum sodium level)
≥130 to <135	3 Consecutive Observations [a]
>125 to <130	2 Consecutive Observations [a]
≤125	1 Observation

a Below upper threshold

All subjects with a serum sodium value <130 mmol/L will be listed by treatment group, including all serum sodium assessments by time-point and including respective demographical data.

Presentations will be done for the overall trial population and by gender.

9.10.3.1 Hyponatraemia during the Randomised Treatment Period

These analyses are restricted to the Safety Analysis Set only.

The incidence of the post-baseline worst-case hyponataemia episode for each subject will be summarised as described in Table 9-6.

Graphs will plot the serum sodium levels by treatment group and the profiles of the subjects who at any time (Visit 1 and onwards) have a serum sodium level <135 mmol/L will be highlighted.

Kaplan-Meier plots of time from randomisation (Visit 4) to hyponatraemic serum sodium levels (<135, <130 and ≤125 mmol/L) per treatment group will be produced. For the thresholds <135 and <130 mmol/L at least 3 and 2 consecutive observations, respectively, have to be below the threshold to yield a hyponatraemic event (Table 9-6). For both cases the time is from randomisation until first observation below the respective limit that counts.

The associated relative hazards of treatment and gender will be analysed using Cox proportional hazards model adjusting for baseline serum sodium and age (<65, ≥65 years). Possible heterogeneity between the genders in the relative treatment hazards will be explored by the inclusion of a treatment-by-gender interaction term.

9.10.4 Safety Laboratory Variables

Laboratory test results and their change from baseline to end-of-trial will be summarised by treatment group for the Safety Analysis Set. The number and percent of subjects with clinically significant laboratory abnormalities will be presented. Shift tables from baseline to end-of-trial visit (categorised as low, normal and high) will be presented by treatment group.

9.11 Interim Analyses

Two kinds of interim analyses are planned in the trial. One is safety-oriented and concerns the monitoring of the serum sodium levels observed during the active run-in period. As described in

All PROs will be captured in the 3-day e-Diary and completed by the subject, either at the trial site (ISI, Bother) or at home just prior to the trial visit (PGI-I, PGI-S), as outlined in Figure 3-2 and Figure 3-3. For PROs completed at home, subjects will be reminded in due time. The 3-day e-Diary, including the PROs will be reviewed for completeness (via the web-portal) by the trial site personnel throughout the trial (Section 6).

In case of missing ISI and Bother assessments, the reason(s) should be recorded by the trial personnel in the eCRF, e.g., subject refusal, lack of time from subject or functional limitation from subject to complete the questionnaire. Handling of missing assessments and missing data will be detailed in the SAP.

10.3.1 Validation of the Nocturia Impact Diary

10.3.1.1 Psychometric Validation

In connection with this trial, the NI Diary will be further tested and validated through anchor-based analyses including the PRO questionnaires PGI-I and PGI-S (Section 7.1.1.3.1) and subjects' perception of change in NI Diary Total Score as captured in exit interviews (Section 10.3.1.2). Details of these analyses are described in a separate PAP. The order of these three e-Diary assessments, all completed at home, should therefore be NI Diary first, PGI-S second and PGI-I last, as described in Section 7.1.1.3.

10.3.1.2 Validation through Exit Interviews

A sample of subjects (from trial sites in the USA) who have completed the trial will be invited to participate in an exit interview within 14 days of attending the end-of-trial visit (Visit 8). Signed informed consent must have been obtained through the ICF for the trial, as appropriate, before participation in the exit interview.

The exact size of the sample will depend on when saturation has been reached. The subjects included will be proportionate to the clinical trial sample distribution with respect to demographic and clinical characteristics. The investigator at the trial site will be asked to complete a Case Report Form that includes specific requirements for recruiting subjects to ensure the correct mix of subjects.

The exit interview is designed to examine the impact of living with nocturia and to assess what a meaningful positive change would be from the subject's perspective in terms of this impact. In the exit interviews, subjects' ratings and perceptions of changes will be collected using qualitative and quantitative methods. These data will be used to aid in understanding what is, from a subject's perspective, a meaningful change threshold for indicating positive improvement in the impact of nocturia on a subject's life, as measured by the NI Diary.

A detailed description of the exit interview is provided in the Exit Interview Protocol, enclosed in Appendix 1.

All exit interviews will be conducted over the telephone by a trained interviewer from [redacted].

relative change over the time in nocturnal diuresis rate (mL/min normalised to time in bed) should be adjusted for body weight and or/body surface area which are both assumed to be constant over a short period of just 1 week. An analysis of individual nocturia subject data found that reducing Nocturnal Urine Volume (NUV) and increasing the duration of antidiuretic action of a V_2-receptor agonist (desmopressin) was a significant predictor for subsequent decrease from baseline in the number of nocturnal voids.

The underlying pathophysiologic mechanism of NP can be driven by either increased FWC, which based on mode of action will be responsive to antidiuretic treatment, or by increased sodium clearance, which differs substantially in mode of action and is governed by Atrial Natriuretic Peptide (ANP) which again is directly and indirectly influenced by the Renin-Angiotensin-Aldosterone System (RAAS).

The aim of the active run-in is (after excluding all other medical causes of NP) to identify subjects with increased FWC which is responsive to V_2-receptor agonism. In addition, safety will be assessed in this period with special emphasis on hyponatraemia.

OBJECTIVES

Primary Objective

- To establish the dose-response of FE 201836 with respect to the number of nocturnal voids in subjects with nocturia due to NP.

Secondary Objectives

- To evaluate responder rates with regards to changes in number of nocturnal voids.
- To psychometrically validate the Nocturia Impact Diary© (NI Diary).
- To evaluate the patient benefit of FE 201836 based on the NI Diary data.
- To evaluate the clinical benefit of FE 201836 based on reduction in nocturnal voiding.
- To evaluate FE 201836 with respect to sleep benefit, i.e., duration of the First Undisturbed Sleep Period (FUSP) and sleep related Patient Reported Outcomes (PROs).
- To evaluate the pharmacodynamic (PD) effect of FE 201836 with respect to nocturnal diuresis rate and NP.

Safety Objective

- To evaluate the safety profile of FE 201836.

Exploratory Objectives

- To explore the biomarker copeptin, an AVP surrogate, to identify low nocturnal vasopressin levels in plasma.
- To explore the dose-response of FE 201836 with respect to total sleep time.
- To explore the association between total sleep time and FUSP.
- To explore the effect of FE 201836 with respect to Nocturnal Polyuria index (NPi).

Definition of Terms

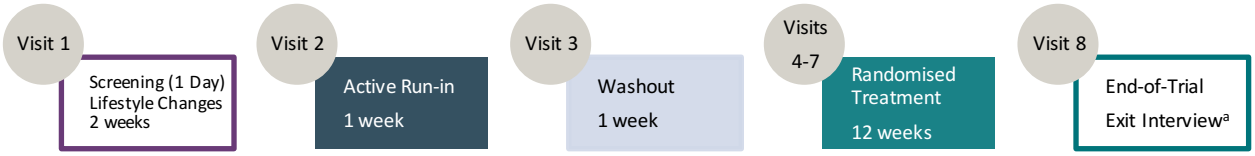
Hyponatraemia	Hyponatraemia is categorised by severity based on serum sodium concentrations: • Normal lower limit of serum sodium ≥135 mmol/L • Mild hyponatraemia: serum sodium 134-130 mmol/L • Moderate* hyponatraemia: serum sodium <130 mmol/L • Severe hyponatraemia: serum sodium ≤125 mmol/L * Moderate hyponatraemia is equivalent to the term 'clinically significant hyponatraemia' (Verbalis, 2013)
Nocturnal diuresis	The nocturnal diuresis rate is calculated from the mean of 3 days Nocturnal Urine Volume (NUV) and total time in bed: $$Nocturnal\ diuresis\ rate\ (mL/min) = \frac{\text{NUV (mL)}}{\text{Total Time in Bed (min)}}$$
FUSP	First Undisturbed Sleep Period (FUSP) is defined as the time in minutes from the time of going to bed to the time of first nocturnal void, or time of awakening if no void occurred.
MED	The lowest dose that has at least a Δ=0.3 larger reduction in mean nocturnal voids as compared to placebo.
ED_{85}	The lowest dose that achieves at least 85% of the effect of the maximum dose.
NPi	Nocturnal Polyuria index (NPi) is calculated by dividing the nocturnal urine volume (NUV) by the 24-hour urine volume (van Kerrebroeck, 2002; Gormley, 2014). In this clinical trial the NPi definition >33% is used for all ages to define presence of Nocturnal Polyuria (NP).
NUV	Nocturnal Urine Volume (NUV) is the total urine volume from 5 minutes after bedtime with the intention to sleep until the first void within 30 minutes of rising (in the morning).
Enrichment period	The enrichment period consists of 1 week active run-in followed by 1 week washout. The enrichment ensures that subjects respond to the drug (reduction in nocturna diureis by ≥20% from Visit 2 to Visit 3) and have a stable condition of ≥2 voids at Visit 2 and Visit 4.

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagrams

A trial overview is presented in Figure 3-1. Overviews of trial visits and electronic diary (e-Diary) assessments and questionnaires to be completed by the subjects before and after randomisation are presented in Figure 3-2 and Figure 3-3.



a A sample of subjects (from trial sites in the USA) who have completed the trial will participate, by telephone, in an exit interview within 14 days of attending Visit 8.

Figure 3-1 Trial Overview

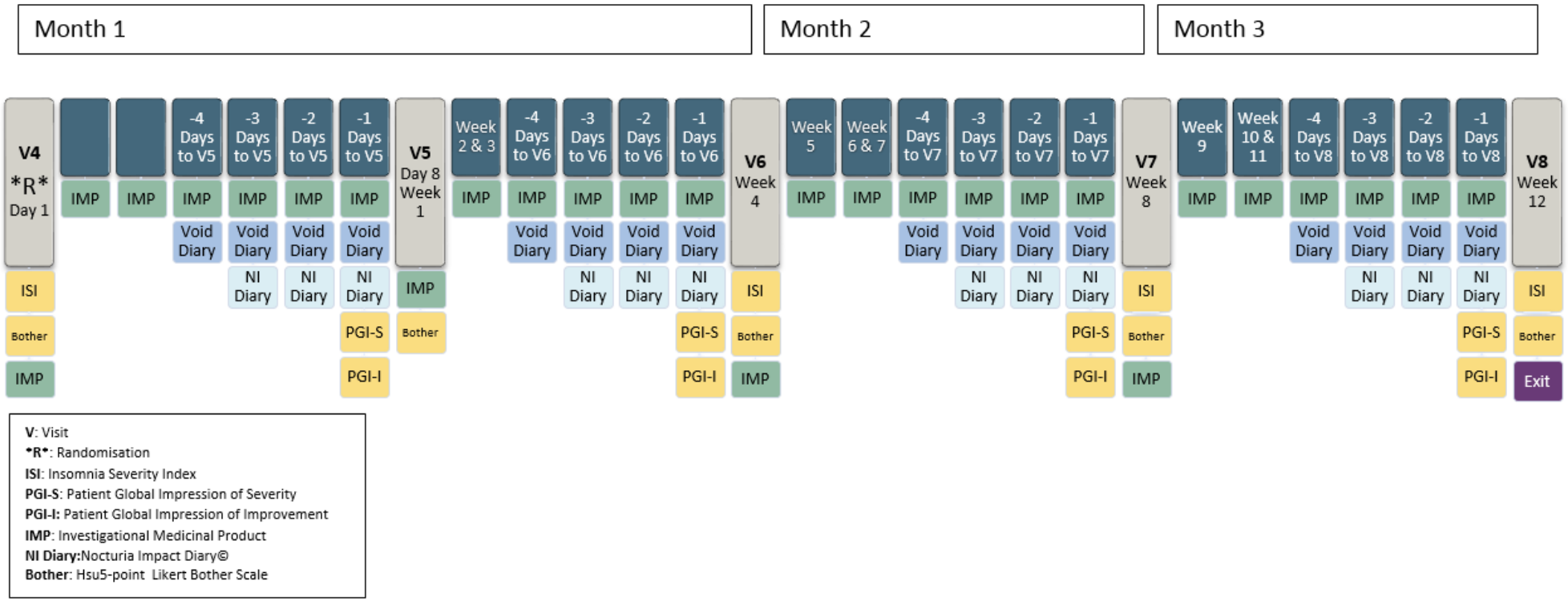


Figure 3-3 e-Diary Assessments and Questionnaires to be Completed by the Subject During the Randomised Treatment Period

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

The trial population will be adult male and female subjects with nocturia due to NP, approximately 50% of each gender, who fulfil the eligibility criteria listed below.

4.1.1 Inclusion Criteria

Each subject must meet the following inclusion criteria between Visit 1 (screening) through Visit 4 (randomisation):

1. Written informed consent prior to performance of any trial-related activity
2. Adults ≥18 years of age (at the time of written consent)
3. Female subjects of child-bearing potential must be willing and able to use adequate contraception throughout the trial. Documentation of an acceptable effective method of contraception must be available. All pre- and perimenopausal subjects have to perform pregnancy tests. Amenorrhea of more than 12 months duration based on the reported date of the last menstrual period is sufficient documentation of post-menopausal status and does not require a pregnancy test
4. Medical history of, or subject reported nocturia symptoms during the 6 months prior to Visit 1
5. ≥2 nocturnal voids (an average over 3 days) as documented in the 3-day e-Diary prior to Visit 2
6. The largest single voided volume must be ≥200 mL (at least 1 void ≥200 mL) as documented in the 3-day e-Diary prior to Visit 2
7. Nocturnal polyuria, defined as NPi >33%, a ratio of NUV in excess of 33% of total daily (24-hour) urine volume as documented in the 3-day e-Diary prior to Visit 2
8. [b]
9. ≥20% decrease in the nocturnal diuresis rate (mL/min) (that was recorded at Visit 2) as documented in the 3-day e-Diary prior to Visit 3
10. Additionally to be randomised into the trial at Visit 4 subjects must have ≥2 nocturnal voids (an average over 3 days) as documented in the 3-day e-Diary prior to Visit 4

[b] Original inclusion criterion omitted as per Clinical Trial Protocol Amendment 02 (applicable for all trial sites).

6.2 Visit 1 Screening

Potential participants will be scheduled to come to the clinic for the screening assessments.

The following must take place during the screening period:

- Signing of informed consent
- Allocation of a screening number
- Inclusion and exclusion criteria will be evaluated.
- Demographic data will be recorded.
- Information on medical history will be recorded based on review of the medical records and interview of the subject.
- Information on concomitant medication will be recorded.
- Physical examination, including body weight and height, will be performed.
- Vital signs (blood pressure and heart rate) will be measured.
- Blood samples will be drawn for analysis of haematology, clinical chemistry (including serum sodium) and coagulation factors.
- Urine samples will be collected for urinalysis.
- Serum and urine pregnancy tests will be performed in all pre- and perimenopausal female subjects.
- Assessment of OSA.
- 12-lead electrocardiogram (ECG) will be measured.
- The e-Diary will be dispensed. Subjects will be trained to complete the e-Diary and will be encouraged to complete the diary at home during 5 days for training purposes.
- The subject will be given instructions about lifestyle changes and will be requested to maintain these lifestyle changes throughout the trial (Section 4.3.3).

The e-Diary training will be followed by the trial site personnel (via the web-portal).

Prior to Visit 2 the subject will be reminded to complete the e-Diary (Section 7.1.1) for 3 consecutive days just prior to the visit.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Endpoints

7.1.1 e-Diary

Subjects will receive an e-Diary for completion containing: a 3-day voiding diary (Section 7.1.1.1), the NI Diary and PRO questionnaires as described in Section 7.1.1.2. The following items are included in the e-Diary:

- Time of daily IMP administration
- 3-Day Voiding Diary
- Nocturia Impact (NI) Diary©
- PRO questionnaires
  - Patient Global Impression of Severity (PGI-S)
  - Patient Global Impression of Improvement (PGI-I)
  - Insomnia Severity Index (ISI)
  - Hsu 5-point Likert Bother Scale

At Visit 1, the subjects will be trained to complete the e-Diary, which they will be encouraged to complete at home for 5 days (Figure 3-2).

If the subject is not able to complete the e-Diary assessments, due to technical issues, prior to Visit 2 (only), it is permitted that the subject repeats the e-Diary assessments.

The e-Diary will be reviewed for completeness by the trial site personnel, via the web portal, throughout the trial.

7.1.1.1 3-Day Voiding Diary

A 3-day voiding diary (included in the e-Diary, Section 7.1.1) will be used to collect information regarding: time of voiding episodes, urine volume, with or without urgency, with or without incontinence and other related information, including time of going to bed and time of awakening in the morning. The subjects will be asked to complete voiding diaries over 3 consecutive 24-hour periods just prior to scheduled visits, as outlined in Table 7-1 and shown in Figure 3-2 and Figure 3-3.

During the 1-week washout period, each subject must complete a 3-day voiding diary to confirm the eligibility for the trial. The voiding diary should be completed over 3 consecutive 24-hour periods just prior to Visit 4.

After randomisation (Visit 4) each subject has to complete four 3-day voiding diaries prior to the scheduled trial visits.

Nocturnal voids are defined as the voids occurring from 5 minutes after bedtime, with the intention to sleep at night, until rising in the morning. The first morning void will not be counted as a nocturnal void even though its volume is included as part of the NUV. The time to first void is defined as the time from bedtime with the intention to sleep until first nocturnal void.

The sponsor will provide the subjects with cups for measuring the urine volume.

Prior to each visit the subjects will receive reminders to complete the e-Diary.

7.1.1.2 Nocturia Impact Diary

Nocturia has wide-ranging implications for patients' quality of life, mainly through persistent, repeated sleep interruptions. Valid patient self-reported assessments of disease burden and benefit of therapy are essential to evaluate the full clinical value of treatment for the patient.

The NI Diary is a validated, nocturia-specific tool available in multiple languages and consists of a 12-item questionnaire with 11 core items (Q1-Q11) and an overall QoL impact question (Q12) (Holm-Larsen, 2014). It is used in conjunction with a voiding diary to capture patient reported consequences of nocturia and its treatment. It has a recall period of one night and day. Responses are scored from 0 to 4 (lowest to highest impact). For Question 12, response options range from 0 (not at all) to 4 (a great deal). The NI Diary total scores are calculated by summing the 11 core items. The NI Diary total and overall impact scores are standardised from 0 to 100 (lowest to highest impact).

The NI Diary will be included in the e-Diary (Section 7.1.1), which will be completed by the subjects at home, for the 3 consecutive days just prior to scheduled visits as outlined in Figure 3-2 and Figure 3-3. The NI Diary should be completed in the evening and before completing the PGI-S and PGI-I questionnaires.

One objective of this trial is to further validate the NI Diary, as well as to establish what constitutes a meaningful change in the NI Diary Total Score. Thus, the disease-specific NI Diary will be further tested and validated in connection with this trial. This will be done through pshychometric validation, as described in Section 10.3.1.1, and through exit interviews, as described in Section 10.3.1.2.

7.1.2 Adverse Events

The procedures for collection and recording of adverse events are described in Sections 8 (Adverse Events) and 8.5 (Serious Adverse Events).

7.1.3 Clinical Laboratory Variables

Urine and blood samples for assessment of safety laboratory values (urinalysis, haematology, coagulation factors and clinical chemistry parameters including serum sodium) will be collected as presented in Table 6-1. A central laboratory will be used for the analyses (Section 7.3). Evaluation of the laboratory-based eligibility criteria will be determined by the central laboratory results. The analytical parameters are listed in Table 7-3.

Details for handling of serum sodium samples are given in Section 7.1.3.1.

Laboratory values will be reported to the investigator. Laboratory reports from the screening visit (Visit 1) must be available for evaluating the inclusion and exclusion criteria prior to the active run-in period (Visit 2) and before randomisation (Visit 4). Measurements outside normal ranges will be assessed by the investigator as 'abnormal, not clinically significant' or 'abnormal, clinically significant'. Any abnormal, clinically significant changes should be reported as adverse events (Section 8.2). The laboratory reports will be signed and dated by the investigator.

Table 7-3 Safety Laboratory Variables

Clinical Chemistry	Haematology	Coagulation	Urinalysis
Alanine aminotransferase Albumin Albumin/Globulin ratio Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Creatinine Creatine phosphokinase Gamma-glutamyl transferase Glucose HbA_{1c} Potassium Sodium Total bilirubin Direct bilirubin Total protein Blood urea nitrogen Uric acid Triglycerides	Haemoglobin Haematocrit Platelet count Red blood cell count White blood cell count with differential count (eosinophils, monocytes, basophils, neutrophils, lymphocytes)	von Willebrand Factor Factor VIII	Blood Glucose Ketones Urinary sediment (erythrocytes, leukocytes) pH Protein Urobilinogen Dipstick assessment and microscopic examination will be performed. A culture will be performed in case of abnormal values.

Any Time Point during the Trial

If the serum sodium value is ≤125 mmol/L at any time point during the trial, the treatment with the IMP must be stopped immediately and the subject must be withdrawn from the trial. All cases of serum sodium values ≤125 mmol/L will be reported as Serious Adverse Event (SAEs) (Section 8.5). The subject will be followed (by the investigator) for safety until the serum sodium level is stable and not clinically significant, preferably until at least ≥135 mmol/L.

Acute Intercurrent Illness

In case of acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis), the treatment with IMP should be interrupted until the subject has fully recovered. The treatment can be re-started at the discretion of the investigator once the condition of the subject is stabilised.

In addition, subjects may be called in for additional unscheduled visits due to safety reason, as described in Section 6.8.

Additional Serum Sodium Testing

Events that will trigger additional serum sodium testing include, but are not limited to, the following:

- If more than 21 days elapse from the serum sodium measurement at Visit 1 and the visit date of Visit 2, the serum sodium measurement must be re-tested, with results available prior to Visit 2.
- A subject is presenting with signs or symptoms of hyponatraemia (e.g., headache, dizziness)
- A subject has gained more than 2 kilograms in body weight between visits (Section 7.2.4)
- If concomitant treatment with therapy that may induce hyponatraemia (Section 4.3.1) is initiated or dosing of an existing therapy is increased during the trial, additional serum sodium monitoring should be performed in the first week (4-8 days) after initiation and again with follow-up as judged by the investigator, at least at 4 weeks.

7.1.3.2 von Willebrand Factor and Factor VIII

Blood samples for assessment of coagulation factors will be collected at Visits 1, 4, 6 and 8.

The concentrations of the coagulation factors von Willebrand Factor (vWF) and Factor VIII (FVIII) were assessed in the phase 1 clinical trial, 000195, after both oral and intravenous administration of FE 201836. The results indicated that both vWF and FVIII were increased at high plasma concentrations of FE 201836. vWF started to increase at a plasma concentration of approximately 150 pg/mL FE 201836 and FVIII at a plasma concentration of approximately 200 pg/mL. Such high plasma concentrations are unlikely to be reached in the urological doses proposed for the present trial, however, vWF and FVIII will be measured as a safety precaution, and to ensure that these coagulation factors are not released in clinically significant amounts.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An adverse event is any untoward medical occurrence in a subject participating in a clinical trial. It includes:

- Any unfavourable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP.
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality, vital sign or finding from physical examination assessed as clinically significant by the investigator (note: pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not adverse events, but are recorded as medical history).
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.
- Overdoses and medication errors with and without clinical consequences.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The investigator must monitor the condition of the subject throughout the trial from the time of obtaining informed consent until the last visit.

The sources of adverse events cover:

- The subject's response to questions about his/her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit).
- Symptoms spontaneously reported by the subject.
- Investigations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities.
- Other information relating to the subject's health becoming known to the investigator (e.g., hospitalisation).

8.2.2 Recording of Adverse Events

The investigator must record all adverse events in the Adverse Event Log provided in each subject's eCRF with information about:

- Adverse event
- Date and time of onset (time can be omitted, if applicable)
- Intensity
- Causal relationship to IMP

Causal Relationship to IMP
The possibility of whether the IMP caused the adverse event must be classified as one of the following:

Reasonable possibility:

There is evidence or argument to suggest a causal relationship between the IMP and the adverse event, i.e., it is an ADR. The ADR may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence.

No reasonable possibility:

There is no reasonable evidence or argument to suggest a causal relationship between the IMP and the adverse event.

Action Taken to IMP
The action taken to the IMP in response to an adverse event must be classified as one of the following:

- No change (medication schedule maintained or no action taken)
- Withdrawn
- Interrupted

Other Action Taken
Adverse events requiring therapy must be treated with recognised standards of medical care to protect the health and well-being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

If medication is administered to treat the adverse event, this medication should be entered in the Concomitant Medication Log.

Date and Time of Outcome
The date and time the subject recovered or died.

Outcome
The outcome of an adverse event must be classified as one of the following:

- Recovered (fully recovered or the condition has returned to the level observed at initiation of trial treatment)
- Recovered with sequelae (resulted in persistent or significant disability/incapacity)
- Recovering (the event is improving)
- Not recovered
- Fatal

The longitudinal data profile used in the simulations is based on pooled data from desmopressin clinical trials FE 992026 CS40 and FE 992026 CS41 (planned treatment group). The following estimates and assumptions were used:

- Dose-response standard deviation $\sigma = 0.95$ voids
- A between to total variance (σ^2) ratio of 0.90 and a true underlying σ of 0.95
- Response fractions of 0.8142, 0.9328 and 0.9874 at Weeks 1, 4 and 8, respectively, as compared to the averaged dose-response at Week 12
- Variance fractions of 0.8481, 0.8329 and 0.8900 at Weeks 1, 4 and 8, respectively, as compared to the averaged dose-response at Week 12

Further design specifications were:

- During the initial 17 weeks the recruitment rate will increase linearly from 0 to 8.2 subjects per week
- After 17 weeks, when all trial sites have been initiated, the recruitment rate is assumed to remain constant at 8.2 subjects per week
- Constant dropout rate of 15% during the randomised treatment period
- First interim analysis when 125 subjects are randomised, thereafter interim analyses every 8 weeks
- Up to the first interim analysis the allocation ratio is 2:2:1 for placebo, 500 µg FE 201836 and desmopressin
- After the first interim analysis the allocation ratios are 2:7:1, for placebo, 50-500 µg FE 201836 and desmopressin
    - Subjects randomised to FE 201836 will be dynamically allotted to 50 µg FE 201836, 100 µg FE 201836, 150 µg FE 201836, 250 µg FE 201836, 350 µg FE 201836 or 500 µg FE 201836 using response-adaptive allocation as outlined in Section 9.11.
- Maximum of 300 randomised subjects

These settings were shared for all treatment groups. The average number of subjects and probabilities for futility and success are presented in Table 9-1.

and σ^2 represents the (total error) variance of the dose-response. The interpretation of the parameters are: α_1 is the placebo response; α_2 is the maximum response; α_3 is the dose (ED_{50}) at which 50% of the maximum effect is obtained; α_4 is the slope parameter.

The longitudinal aspect of the average change from baseline is captured by the following model:

$$Y_{t,i} \sim N(e^{\gamma_t}(\mu_{d,i} + \delta_i), \lambda_t^2),$$

where the per-subject offset from the mean dose-response is $\delta_i \sim N(0, \tau^2)$ and λ_t^2 represents the within subject variance. The model is constrained such that $\alpha_4 = 0$ and the intermediate values of $y_.$ can thus be thought of as being fractions of final value.

Missing data (missing due to drop-out or final visit has not occurred yet) will be imputed using the longitudinal model, assuming missing at random. This implies that also data from subjects who have not yet been observed at Week 12 are used in the primary efficacy analysis, as described in Appendix 2.

All parameters in the models are given sufficiently non-informative prior distributions as specified in Appendix 2. By application of Bayes' theorem and Markov chain Monte Carlo sampling techniques the posterior probabilities (or the quantities of interest) given in Table 9-2 can be estimated.

Table 9-2 Quantities of Interest

Quantity of Interest	Probability Within the Trial That:	Objective
$\Pr(\mu_{MAX} < \mu_{Plb})$	the dose with the maximum effect (i.e. the dose that is *most likely* to have the maximum effect) is superior to placebo	Proof-of-Concept
$\Pr(\mu_{MAX} - \mu_{Plb} < -0.3)$	the dose with the maximum effect (i.e. the dose that is *most likely* to have the maximum effect) has >0.3 voids reduction in nocturnal voids as compared to placebo	Futility
Pr(dose *d* is MED)	dose *d* is the minimum dose that has >0.3 voids reduction in nocturnal voids as compared to placebo	Establish the MED
$\Pr(\text{dose } d \text{ is } ED_{85})$	dose *d* is the minimum dose that has > 85% of the treatment effect of the maximum effective dose	Establish ED_{85}

Table 9-4 Analysis of Endpoints

Efficacy Endpoint	Analysis category				
	Bayesian Estimation of Dose-response Curve	Repeated measures ANCOVA	Correlation Analysis	Repeated logistic regression (Generalized Estimating Equation [GEE])	ANCOVA
Change from baseline in number of nocturnal voids [a]	Primary	Secondary [e]			
Responder rate defined as 50% reduction in nocturnal voids from baseline [a]	Secondary			Secondary	
Change from baseline in NI Diary Total Score [a]	Secondary	Secondary			
Percentage of nights during treatment period with at most one nocturnal void [i]					Secondary
Percentage of nights during treatment period with complete response [i]					Secondary
Change from baseline in NI Diary Overall Impact Score [a]	Secondary	Secondary			
PGI-I urinary symptoms score [a,b]		Secondary			
Change from baseline in PGI-S score [a]		Secondary			
Change from baseline in Bother as measured by the Hsu 5-point Likert Bother Scale [a]		Secondary			
Change from baseline in ISI [f]		Secondary			
Change from baseline in FUSP [a]	Secondary	Secondary	Explorative [h]		
Change from baseline in nocturnal diuresis rate (hourly) [c]		Secondary			
Change from baseline in NUV [c]	Secondary	Secondary			
Responder rates defined as 33%, 60%, 70%, 80%, 90% and 100% reduction from baseline in number of nocturnal voids [a]				Explorative	
Responder rates defined as 1, 2, and 3 voids reduction from baseline in number of nocturnal voids [a]				Explorative	
Copeptin levels at Visit 2			Explorative [g]		
Change from baseline in copeptin levels [d]					Explorative
Change from baseline in total sleep time per night [a]		Explorative			
Change from baseline in NPi [c]		Explorative			
Safety Endpoints					
Change from baseline in mean 24-hour urine volume [c]		Safety			
Incidence and severity of Adverse Events	Section 9.10.2				
Adverse Event of Special Interest: Hyponatraemia Episodes	Section 9.10.3				
Clinically significant changes in vital signs and laboratory values	Sections 9.10.1 and 9.10.4				

a. Endpoint assessed at Weeks 1, 4, 8 and 12 weeks of treatment.
b. This questionnaire is retrospective and raw scores will be used in the analysis (not changes from baseline) and the ANCOVA model will not be adjusted for baseline value.
c. Endpoint assessed at Week 1 and 12 weeks of treatment.
d. Endpoint assessed at 12 weeks of treatment.
e. Sensitivity analysis placebo pattern-mixture models.
f. Endpoint assessed at Week 4, 8 and 12.
g. Correlation with NPi at Visit 2.
h. Correlation between changes in FUSP and total sleep time at Visits 1, 4, 8 and 12.
i. Endpoints are derived using all diary data collected during the treatment period.

Section 3.4, a DMC will be established for the trial and make recommendations based on review of safety data, e.g., increased rates of clinically significant serums sodium levels observed during the active run-in period, as described in Section 9.11.1. The second kind concerns the pre-planned efficacy analyses upon which the trial may be stopped due to futility, or allocation probabilities to FE201836 doses may be adjusted based on estimated dose-response curve, as described in Section 9.11.2.

9.11.1 Serum Sodium Monitoring during the Active Run-In Period

The risk of subjects developing hyponatraemia will be mitigated by a serum sodium monitoring plan (Section 7.1.3.1), including a 1-week active run-in period to identify subjects at increased risk for developing acute hyponatraemia prior to randomisation. If the incidence of serum sodium levels <130 mmol/L is statistically significantly >10% during the active run-in, the DMC (Section 3.4) will be notified and further action will be discussed, e.g., the DMC may recommend that the highest dose of FE 201836 may be replaced by a lower dose.

The number of cases of serum sodium levels <130 mmol/L resulting in an estimated rate that is statistically significantly >10% depends on the number of subjects who have completed the active run-in, examples are presented in Table 9-7.

Table 9-7 Examples of Incidence Rates that are Statistically Significantly >10%

Number of Subjects who have Completed 1-week Active-run in	Number of Cases Observed with Serum Sodium levels <130 mmol/L	Estimate of Incidence Rate	Lower Limit of 95% Confidence Interval
10	4	40%	12.2%
20	6	30%	11.9%
50	10	20%	10.0%
100	17	17%	10.2%
200	30	15%	10.4%

Thus, the present trial has been designed with the option to decrease the maximal dose of FE 201836 from 500 µg to 350 µg if recommended by the DMC. If this decision is made, randomisation to the 500 µg FE 201836 treatment group will be closed, the trial will continue with 350 µg FE 201836 as the highest dose for the active run-in and the highest dose of FE 201836 that any subject can be randomised to. In the case where subjects have already been randomised to 500 µg FE 201836 and have not completed the trial the DMC will recommend whether or not, these subjects may be permitted to remain on 500 µg FE 201836 treatment for the remainder of the trial.

If the decision to close randomisation to 500 µg FE 201836 occurs prior to the first interim analysis (when the first 125 subjects are randomised) the remaining subjects will be randomised to the following treatment groups: placebo, desmopressin (25 µg for females and 50 µg for males) or 350 µg FE 201836. After the interim analysis subjects may be randomised to one of 7 treatment groups: placebo, 50 µg FE 201836, 100 µg FE 201836, 150 µg FE 201836, 250 µg FE 201836, 350 µg FE 201836, or desmopressin (25 µg for females and 50 µg for males).

10.4 Data Management

A data management plan will be prepared under the responsibility of the Global Biometrics Department at Ferring Pharmaceuticals A/S. The data management plan will be issued before data collection begins and will describe all functions, processes and specifications for data collection, cleaning and validation.

10.5 Provision of Additional Information

On request, the investigator will provide the sponsor with additional data relating to the trial, duly anonymised and protected in accordance with applicable requirements.