FERRING
PHARMACEUTICALS

Protocol

Title of trial: A Randomised, Double-blind, Placebo-controlled, Response-adaptive Dose-finding Trial Investigating the Efficacy, Safety and Tolerability of Oral Doses of FE 201836, with Desmopressin Orally Disintegrating Tablet as a Benchmark, During 12 Weeks of Treatment for Nocturia due to Nocturnal Polyuria in Adults
NCT number: NCT03201419
Sponsor trial code: 000233
Date: 05 Jul 2018

CLINICAL TRIAL PROTOCOL

A Randomised, Double-blind, Placebo-controlled, Response-adaptive Dose-finding Trial Investigating the Efficacy, Safety and Tolerability of Oral Doses of FE 201836, with Desmopressin Orally Disintegrating Tablet as a Benchmark, During 12 Weeks of Treatment for Nocturia due to Nocturnal Polyuria in Adults

000233

DAWN

EudraCT Number:	2016-003851-31
IND Number:	129355
Investigational Medicinal Product:	FE 201836
Indication:	Nocturia due to Nocturnal Polyuria
Phase:	2
Name and Address of Sponsor:	Ferring Pharmaceuticals A/S Global Clinical R&D Kay Fiskers Plads 11 2300 Copenhagen S, Denmark Tel: +45 8833 8834
Version:	5.0 (consolidated protocol; changes introduced with global amendments #01, #02, and #03 implemented)
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A Randomised, Double-blind, Placebo-controlled, Response-adaptive, Dose-finding Trial Investigating the Efficacy, Safety and Tolerability of Oral Doses of FE 201836, with Desmopressin Orally Disintegrating Tablet as a Benchmark, During 12 Weeks of Treatment for Nocturia due to Nocturnal Polyuria in Adults

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TRIAL SITES

Approximately 70 sites in Europe and North America.

PLANNED TRIAL PERIOD

First subject first visit: Q3 2017
Last subject last visit: Q3 2019

CLINICAL PHASE

Phase 2

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

Nocturia is defined by the International Continence Society (ICS) as waking from sleep (during the night) at least once to urinate. This may occur when there is an excessive urine production during the night (nocturnal polyuria [NP]). The antidiuretic hormone arginine vasopressin (AVP) plays a key role in the control of urine production during the night. Desmopressin, a synthetic analogue of AVP developed by Ferring Pharmaceuticals, is approved and used for the treatment of nocturia due to NP in more than 80 countries, including Canada and European countries. However, desmopressin has not yet been approved for this indication in the USA.

Low doses of desmopressin (25 µg for women and 50 µg for men) are approved to date in Canada, Australia and European countries under the trade name NOCDURNA (desmopressin Orally Disintegrating Tablet [ODT]). These gender specific minimum effective low doses are approved for use in all adult ages and are indicated for treatment of nocturia due to NP in adults, who awaken two or more times each night to void. The global cumulative patient exposure of NOCDURNA by end-2016 is 1,389 patient years based on a dose of 25 µg for women and 50 µg for men (women: 779 patient years; men: 610 patient years). Analysis of the combined data from three trials of low-dose desmopressin ODT, comprising >1400 patients with nocturia, shows that desmopressin dose, patient age, baseline serum sodium levels, and kidney function according to estimated

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

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).

- To benchmark the efficacy of FE 201836 in relation to desmopressin.

ENDPOINTS

Primary Endpoint

- Change from baseline in number of nocturnal voids during 12 weeks of treatment.

Secondary Endpoints

- Change from baseline in number of nocturnal voids at Weeks 1, 4, 8 and 12.
- Responder rate defined as 50% reduction in nocturnal voids from baseline at Weeks 1, 4, 8 and 12 and during 12 weeks of treatment.
- Change from baseline in NI Diary Total Score at Weeks 1, 4, 8 and 12 and during 12 weeks of treatment.
- Percentage of nights during the treatment period with at most one nocturnal void.
- Percentage of nights during the treatment period with complete response, i.e., with no nocturnal voids.
- 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 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 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.

METHODOLOGY

This is a randomised, double-blind, placebo-controlled, response-adaptive, dose-finding trial investigating the efficacy, safety and tolerability of 6 different oral doses (50-500 µg) of FE 201836, with desmopressin as a benchmark, during 12 weeks of treatment for nocturia due to NP in adults.

The trial will comprise 8 visits to the clinic and will consist of a 2-week screening/lifestyle changes period where no Investigational Medicinal Product (IMP) will be given, an enrichment period consisting of a 1-week single-blind (to subjects) active run-in period and a 1-week washout period, and a 12-week double-blind randomised treatment period for each subject. During the active run-in period the trial subjects will receive 500 µg FE 201836 and placebo to assess safety and establish that subjects who respond to treatment with FE 201836 are included in the trial (i.e., an enrichment design).

The 12-week double-blind randomised treatment period of the trial will follow a response-adaptive Bayesian top-down design. Initially subjects will be randomised to: placebo, 500 µg FE 201836 or desmopressin (for benchmarking only). When approximately 125 subjects have been randomised to the trial, an interim analysis will be conducted to investigate the efficacy of 500 µg FE 201836. If 500 µg FE 201836 is not sufficiently efficacious compared to placebo the trial will be stopped for futility. If 500 µg FE 201836 is efficacious additional doses of FE 201836 (doses 50-350 µg) will be opened up for randomisation of new subjects in order to identify the Minimum Effective Dose (MED) and near maximal Effective Dose (ED_{85}). The ED_{85} is the lowest dose that achieves at least 85% of the effect of the maximum dose (500 µg). After the first interim analysis, subsequent interim analyses will take place every 8 weeks to reassess the randomisation allocation probabilities to 50-500 µg FE 201836, based on observed responses at the respective interim locks.

After the first interim analysis eligible subjects will be randomised to one of 8 treatment groups (Table S-1). Each subject will be instructed to take the IMP every night at bedtime with the intention to sleep. In order to keep the treatment blinded each subject will receive two medications throughout the trial; an oral solution and an Orally Disintegrating Tablet (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.

Subjects will be asked to follow lifestyle changes (e.g., limiting fluid intake) throughout the entire

duration of the trial. In addition, subjects will be asked to complete electronic diary (e-Diary) assessments and Patient Reported Outcome (PRO) questionnaires before and after randomisation. One objective of the present trial is to further validate the NI Diary. Therefore, 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), to record the subjects' perception of what constitutes a meaningful change in the NI Diary Total Score.

Safety, including serum sodium levels, 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).

Furthermore, the risk for subjects developing hyponatraemia will be mitigated by a serum sodium monitoring plan, 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 Data Monitoring Committee (DMC) 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.

NUMBER OF SUBJECTS

A maximum of 300 subjects (males and females) will be randomised into the trial. At least 50% of subjects should be randomised at trial sites in the USA.

CRITERIA FOR INCLUSION / EXCLUSION

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

Exclusion Criteria

Any subject meeting one or more of the following exclusion criteria between Visit 1 (screening) through Visit 4 (randomisation) will be considered as a screening failure:

1. Current diagnosis of Obstructive Sleep Apnoea (OSA)
2. Restless Legs Syndrome (RLS)
3. Suspicion of Bladder Outlet Obstruction (BOO) or urine flow <5 mL/s, as confirmed by uroflowmetry during screening prior to Visit 2
4. Urinary incontinence defined as an average of >1 episode/day in the 3-day e-Diary prior to Visit 2 (occasional urge incontinence during daytime or at night on the way to void is not necessarily exclusionary)
5. [c]
6. Any pelvic or lower urinary tract surgery and/or radio therapy or previous pelvic irradiation within the past 6 months prior to Visit 1. Including e.g., transurethral resection for BOO or Benign Prostatic Hyperplasia (BPH), hysterectomy or female incontinence procedures
7. Genito-urinary tract pathology that can in the investigator's opinion be responsible for urgency or urinary incontinence e.g., symptomatic or recurrent urinary tract infections, interstitial cystitis, bladder-related pain, chronic pelvic pain syndrome, or stone in the bladder or urethra causing symptoms
8. A history of cancer with the last date of disease activity/prescence of malignancy within the last 12 months prior to Visit 1, except for adequately treated basal cell carcinoma of the skin
9. History of any neurological disease affecting bladder function or muscle strength (e.g., Multiple Sclerosis, Parkinson's, spinal cord injury, spina bifida)
10. Habitual (fluid intake >3L per day) or psychogenic polydipsia
11. Uncontrolled hypertension, as judged by the investigator

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

[c] Original exclusion criterion omitted as per Clinical Trial Protocol Amendment 03 (applicable for all trial sites).

12. [a]
13. Uncontrolled diabetes mellitus, as judged by the investigator
14. Central or nephrogenic diabetes insipidus
15. Known history of Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion
16. History of gastric retention
17. Suspicion or evidence of congestive heart failure, (New York Heart Association [NYHA] class II, III, IV)
18. Hyponatraemia:
    - Serum sodium level <135 mmol/L at Visit 1(re-tested, with results available within 7 days)
    - Serum sodium level <130 mmol/L at Visit 3 (re-tested, with results available within 7 days)
19. Hepatic and/or biliary diseases:
    - Child-Pugh Class A, B, or C

      or
    - Aspartate aminotransferase and/or alanine aminotransferase levels >3x the upper limit of normal range as well as total bilirubin level >2x the upper limit of normal range
20. Known history of hypersensitivity to desmopressin ODT
21. Pregnancy, breastfeeding, or a planning to become pregnant during the period of the trial
22. Known alcohol or substance abuse
23. Work or lifestyle that may interfere with regular night-time sleep e.g., shift workers
24. Any other medical condition, laboratory abnormality, psychiatric condition, mental incapacity, or language barrier that, in the judgment of the investigator, would impair participation in the trial
25. [d]
26. Previous participation in a nocturia, Benign Prostatic Obstruction (BPO), or OAB clinical trial within the past 6 months prior to Visit 1
27. The subject is in a state of dependence of the sponsor, or is directly or indirectly involved in the conduct of this trial as an investigator, sub-investigator, trial coordinator or other trial staff member, or the subject is a first degree family member, significant other or relative residing with one of the above persons involved directly or indirectly with the trial

[a] Original exclusion criterion omitted as per Clinical Trial Protocol Amendment 01 (applicable for all trial sites).

[d] Original exclusion criterion omitted as per Clinical Trial Protocol Amendment 03 (applicable for all trial sites).

28. Use of any restricted therapy not in accordance with the protocol

29. Use of any prohibited therapy listed below:
    - Current or former (within 3 months prior to screening) treatment with any other IMP
    - Unstable electrostimulation or behavioural bladder training program less than 3 months prior to screening (stable electrostimulation or behavioural bladder training program started at least 3 months before screening are acceptable)
    - Thiazide diuretics
    - Antiarrhythmic agents
    - V_2-receptor antagonists/agonists (e.g., vaptans/desmopressin, vasopressin)
    - Loperamide
    - Botulinum toxin (cosmetic non-urological use is acceptable)
    - Valproate

INVESTIGATIONAL MEDICINAL PRODUCTS

In order to maintain the treatment blinding each subject will receive 2 medications (a double-dummy design), an oral solution and an ODT formulation, during every treatment period of the trial, as outlined in Table S-1.

Table S-1 Treatment During the Trial

Treatment	Investigational Medicinal Product	
	Active Substance	Placebo
Active Run-in		
500 µg FE 201836	500 µg FE 201836 oral solution	Placebo ODT
Washout		
-	-	-
Randomised Trial Period		
Up to First Interim Analysis		
500 µg FE 201836	500 µg FE 201836 oral solution	Placebo ODT
Desmopressin	Desmopressin ODT (25µg for females and 50 µg for males)	Placebo oral solution
Placebo	-	Placebo oral solution and Placebo ODT
After First Interim Analysis		
50 µg FE 201836	50 µg FE 201836 oral solution	Placebo ODT
100 µg FE 201836	100 µg FE 201836 oral solution	Placebo ODT
150 µg FE 201836	150 µg FE 201836 oral solution	Placebo ODT
250 µg FE 201836	250 µg FE 201836 oral solution	Placebo ODT
350 µg FE 201836	350 µg FE 201836 oral solution	Placebo ODT
500 µg FE 201836	500 µg FE 201836 oral solution	Placebo ODT
Desmopressin	Desmopressin ODT (25µg for females and 50 µg for males)	Placebo oral solution
Placebo	-	Placebo oral solution and Placebo ODT

DURATION OF TREATMENT

The duration of the trial is approximately 16 weeks. Subjects will be screened, enter a 2-week lifestyle changes period followed by a 1-week single-blind active run-in and 1-week washout prior to randomisation. Following randomisation, the first 125 subjects will be treated daily with placebo, 500 µg FE 201836 or desmopressin (25 µg for females and 50 µg for males) for up to 12 weeks. When the first 125 subjects have been randomised an interim analysis will be conducted and a decision taken on whether to continue the trial as planned or stop the trial for futility.

If the decision is to continue the trial as planned, subjects may be randomised to one of 8 treatment groups for 12 weeks: placebo, 50 µg FE 201836, 100 µg FE 201836, 150 µg FE 201836, 250 µg FE 201836, 350 µg FE 201836, 500 µg FE 201836, or desmopressin (25 µg for females and 50 µg for males).

STATISTICAL METHODS

Primary Analysis Model used in the Response-adaptive Trial Design

The primary analysis is based on a time-course hierarchical longitudinal model, i.e.,

$$Y_{t,i} = e^{\gamma_t}(\mu_{d,i} + \delta_i) + \varepsilon_t$$

where $Y_{t,i}$ is the change from baseline in number of nocturnal voids at visit t for subject i, d is the dose, e^{γ_t} the fraction of the effect at Visit t (Week 1, Week 4 or Week 8) as compared to the Month 3 visit (γ_t=0 at Month 3), δ_i the random subject effect and ε_t the independent N(0, λ_t^2) distributed error term. The dose-response for subject i, $\mu_{d,i}$, is adjusted for the number of baseline voids ($x_{0,i}$) and modelled using the sigmoidal E-max model, i.e.,

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

Inference will be based on a Bayesian analysis using sufficiently non-informative priors on respective parameters. The trial will be considered successful if the maximum dose has a greater than 97.5% posterior probability of being better than placebo, i.e., if $Pr(\mu_{MAX} < \mu_{Plb}) > 97.5\%$.

Response-adaptive Decision Rules

The double-blind treatment period is based on a response-adaptive Bayesian top-down design. After an initial 125 subjects have been randomised to placebo, 500 µg FE 201836 **(**the highest dose) or desmopressin in a 2:2:1 ratio an interim analysis will take place to stop for futility if the $Pr(\mu_{MAX} - \mu_{Plb} < -0.3) < 10\%$, where Pr (.) denotes posterior probability (under the assumed monotonic dose-response relation, i.e. smaller doses will be less effective).

If not stopped for futility, all treatment arms will be opened up for randomisation, subjects can be randomised to placebo, desmopressin or to any FE 201836 dose (50-500 µg) in a 2:1:7 ratio. When allocated to a FE 201836 dose (7/10), unrestricted randomisation will be used to allocate a subject

to a specific FE 201836 dose using an allocation probability that is the average of *I*(dose is MED) and *I*(dose is ED_{85}), where *I*(target) is the probability that "dose is target" scaled by the squared standard error at that dose. The MED is the lowest dose that has at least a Δ=0.3 larger reduction in mean nocturnal voids as compared to placebo and the ED_{85} is the lowest dose that achieves at least 85% of the effect of the maximum dose (500 µg).

After the first interim analysis, subsequent interims will take place every 8 weeks where the randomisation allocation probabilities to FE 201836 doses are being updated. Futility stopping will remain to take place if $Pr(\mu_{MAX} - \mu_{Plb} < -0.3) < 5$.

Operating Characteristics

Under the assumptions (based on previous desmopressin trials and feasibility) that:

- 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
- A constant drop-out rate of 15% during the randomised treatment period
- A between to total variance (σ^2) ratio of 0.90 and a true underlying σ of 0.95
- 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

and

- Considering six dose-response scenarios for the mean change from baseline to a large extent is characterised by the response of the maximum dose (500 µg FE 201836)

Given these assumptions the operating characteristics presented in Table S-2 apply:

Table S-2 Operating Characterisitics

Dose-Response Scenario	Maximum response (α_2)	ED_{50} (α_3)	Average Number of Subjects	Futility Stopping at First Interim	Total Futility stopping	**Power** (Total Success)
Null	0	0 µg	200	75.8%	97.0%	**3.0%**
I	-0.3	150 µg	277	15.7%	47.9%	52.1%
II	-0.4	200 µg	288	7.9%	25.1%	74.9%
III	-0.5	200 µg	296	2.8%	9.6%	**90.4%**
IV	-0.5	350 µg	295	3.4%	15.4%	**84.6%**
V	-0.6	300 µg	298	1.4%	2.7%	97.3%

For each dose-response scenario, 1,000 trials were simulated in order to estimate the operating characteristics presented in Table S-2. Assuming a maximum reduction versus placebo of 0.5 voids

the power (probability of success) reaches approximately 85 to 90%, while the probability of making a false positive conclusion is 3.0%.

Randomisation if the Maximum Dose is Lowered

The trial has been designed with the option to decrease the maximum 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. In case subjects randomised to treatment with 500 µg FE 201836 prematurely discontinue the trial due to DMC decision they may be replaced by subjects randomised to treatment with a lower dose of FE 201836. No other prematurely discontinued subjects will be replaced.

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 first interim analysis the dose-response adaptive randomisation will allocate subjects to the remaining open doses, i.e., 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).

The dose-response model will be fitted across all doses, i.e., 0-500 µg, but inference will be made only on the doses that remain open to randomisation e.g., 0-350 µg. That is, the MED and ED_{85} doses and the inferences with regards to proof-of-concept and futility are limited to the dose range (i.e, with a maximum dose of 350 µg FE 201836).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

ADR	Adverse Drug Reaction
ANCOVA	Analysis of Covariance
ANP	Atrial Natriuretic Peptide
ATC	Anatomical Therapeutic Chemical Classification System
AUA	American Urology Association
BOO	Bladder Outlet Obstruction
BPO	Benign Prostatic Obstruction
BPH	Benign Prostatic Hyperplasia
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
e-Diary	Electronic Diary
ED_{85}	The near (≥85%) maximal Effective Dose
EU	European Union
FACTS	Fixed and Adaptive Clinical Trial Simulator
FAS	Full Analysis Set
FDA	Food and Drug Administration
FWC	Free Water Clearance
FUSP	First Undisturbed Sleep Period
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISI	Insomnia Severity Index
ITT	Intention-to-Treat analysis set for the randomised treatment period
ITT-ENR	Intention-to-Treat analysis set for the enrichment period

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

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.

1 INTRODUCTION

1.1 Background

Nocturia is defined by the International Continence Society (ICS) as waking from sleep (during the night) at least once to urinate. Nocturia is a symptom complex associated with several underlying medical and urological causes and pathologies (van Kerrebroeck, 2002; Wein, 2002). It is common in the elderly, occurring in up to 50% of men and women older than 75 years (Bosch, 2010).

Nocturia is associated with a variety of clinical syndromes and disorders, which may result from (van Kerrebroeck, 2002):

- Disorders that cause frequent low volume voids (e.g., Overactive Bladder [OAB], Bladder Outlet Obstruction [BOO], stiffer/less-compliant/functionally-smaller bladder associated with aging)

  or

- frequent high volume voids (e.g., Nocturnal Polyuria [NP], global polyuria [diabetes insipidus or mellitus])

  or

- a combination of both, which is common.

As described above, NP is a subset of nocturia defined as excessive volume of urine produced at night. The human body typically produces less urine while asleep. People with NP produce larger volumes of urine when asleep, causing them to awaken multiple times in the night to void. Thus, the diagnosis nocturia may be applied when there is an excessive urine production during the night.

Nocturnal polyuria has been attributed to:

- Abnormalities in diurnal variation in vasopressin secretion (a condition also coined as NP syndrome) (Asplund, 1991)
- Abnormalities in the diuresis of solutes (e.g., urea, sodium, potassium)
- Night time mobilisation of oedematous fluid in conditions such as congestive heart failure, nephrotic syndrome, or venous insufficiency

However, as described above, patients often have more than one symptom presenting as nocturia (or NP); e.g., high volume of urine at night in combination with low volume bladder (perhaps associated with ageing) and BOO.

Taken together, these facts make the clinical situation complicated since patients may have NP overlaid symptoms associated with frequent, low-volume voids, including OAB and Benign Prostatic Hyperplasia (BPH).

The antidiuretic hormone arginine vasopressin (AVP) plays a key role in the control of urine production during the night. Desmopressin, a synthetic analogue of AVP developed by Ferring Pharmaceuticals, is approved and used for the treatment of nocturia due to NP in more than

80 countries, including Canada and European countries. However, desmopressin has not yet been approved for this indication in the USA.

Low doses of desmopressin (25 µg for women and 50 µg for men) are approved to date in Canada, Australia and European countries under the trade name NOCDURNA (desmopressin Orally Disintegrating Tablet [ODT]). These gender specific minimum effective low doses are approved for use in all adult ages and are indicated for treatment of nocturia due to NP in adults, who awaken two or more times each night to void. The global cumulative patient exposure of NOCDURNA by end-2016 is 1,389 patient years based on a dose of 25 µg for women and 50 µg for men (women: 779 patient years; men: 610 patient years). Analysis of the combined data from three trials of low-dose desmopressin ODT, comprising >1400 patients with nocturia, shows that desmopressin dose, patient age, baseline serum sodium levels, and kidney function according to estimated glomerular filtration rate clearance were significant risk factors for hyponatraemia in both sexes (Juul, 2016).

Ferring Pharmaceuticals 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 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 only). 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 potentially 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 selection of FE 201836 doses in the trial is based on 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 a phase 1 trial (000195) in young healthy men and women, oral doses of FE 201836 of up to 4,800 µg 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).

1.2 Scientific Justification for Conducting the Trial

Concern over hyponatraemia and the risk-benefit ratio has limited the use of desmopressin to younger patients and recently allowing treatment in elderly nocturia patients only under serum sodium monitoring. Renal impairment has also limited the use due to a risk of prolonging duration of action. FE 201836, a novel short-acting V_2-receptor agonist, now under development, is designed to preserve potency at the V_2-receptor at the same level as desmopressin, with a shorter half-life, increased selectivity, faster clearance and greater extra-renal clearance compared to desmopressin.

The present phase 2 trial will establish the dose-response of FE 201836 with respect to the number of nocturnal voids in subjects with nocturia due to NP, allowing the development to proceed for a novel agonist at the V_2-receptor for treatment of nocturia due to NP.

1.3 Benefit / Risk Aspects

Benefits

Subjects enrolled in the present trial will be closely monitored and they will have the same or more frequent visits to the hospital compared to routine treatment, depending on local practice. During these visits the subjects will be given instructions regarding lifestyle changes (including limiting fluid intake). For some subjects the implementation of lifestyle changes might be enough to reduce bothersome nocturia, defined as 2 or more nocturnal voids.

Risks

Treatment of nocturia due to NP with desmopressin implies a prolonged antidiuretic effect that may be associated with an increased risk of developing hyponatraemia, especially in elderly patients. FE 201836 is designed to preserve potency at the V_2-receptor at the same level as desmopressin, with a shorter half-life, increased selectivity, faster clearance and greater extra-renal clearance compared to desmopressin. Based on the low degree of unchanged renal excretion of FE 201836, renal impairment is not expected to have any clinically relevant impact on the duration of the antidiuretic effect.

An improved safety profile is expected to result from this combination of characteristics. The short half-life of FE 201836 (approximately 2 hours) and low degree of unchanged renal excretion (approximately 5%) are designed to limit the antidiuretic effect to the night-time sleep period, when subjects do not drink or their fluid intake is limited to a minimum (to satisfy thirst only). Therefore, the risk for dilutional hyponatraemia that may occur after the subject starts drinking in the morning is expected to be low.

Subjects in the phase 1 clinical trial 000195 were dosed with up to 4800 µg (i.e., 9.6 times higher than the suggested maximum dose in the present phase 2 trial) orally without any subject being hyponatraemic. Pharmacokinetic/pharmacodynamic (PK/PD) modelling suggests that the duration of antidiuretic effect at 500 µg will be approximately 6 hours, limiting the potential for daytime antidiuresis.

In the present trial, the risk of subjects developing hyponatraemia will be mitigated by a serum sodium monitoring plan, as described in Section 7.1.3.1. The plan includes a 1-week active run-in period to identify subjects at increased risk for developing acute hyponatraemia prior to randomisation, as well as serum sodium sampling at Week 1, Week 4, Week 8 and Week 12, to identify any subject developing hyponatraemia while on treatment with Investigational Medicinal Product (IMP). Moreover, safety including the occurrence of adverse events and clinically significant changes in laboratory values (including serum sodium values) will be monitored throughout the trial.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 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 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).
- To benchmark the efficacy of FE 201836 in relation to desmopressin.

2.2 Endpoints

Primary Endpoint

- Change from baseline in number of nocturnal voids during 12 weeks of treatment.

Secondary Endpoints

- Change from baseline in number of nocturnal voids at Weeks 1, 4, 8 and 12.
- Responder rate defined as 50% reduction in nocturnal voids from baseline at Weeks 1, 4, 8 and 12 during 12 weeks of treatment.
- Change from baseline in NI Diary Total Score at Weeks 1, 4, 8 and 12 and during 12 weeks of treatment.
- Percentage of nights during the treatment period with at most one nocturnal void.
- Percentage of nights during the treatment period with complete response, i.e., with no nocturnal voids.

- 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

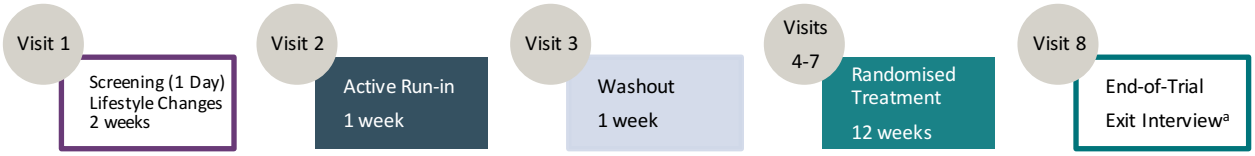
- Responder rates defined as 33%, 60%, 70%, 80%, 90% and 100% reduction from baseline in number of nocturnal voids at Weeks 1, 4, 8 and 12.
- Responder rates defined as 1, 2, and 3 voids reduction from baseline in number of nocturnal voids at Weeks 1, 4, 8 and 12.
- The correlation of copeptin levels 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.

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

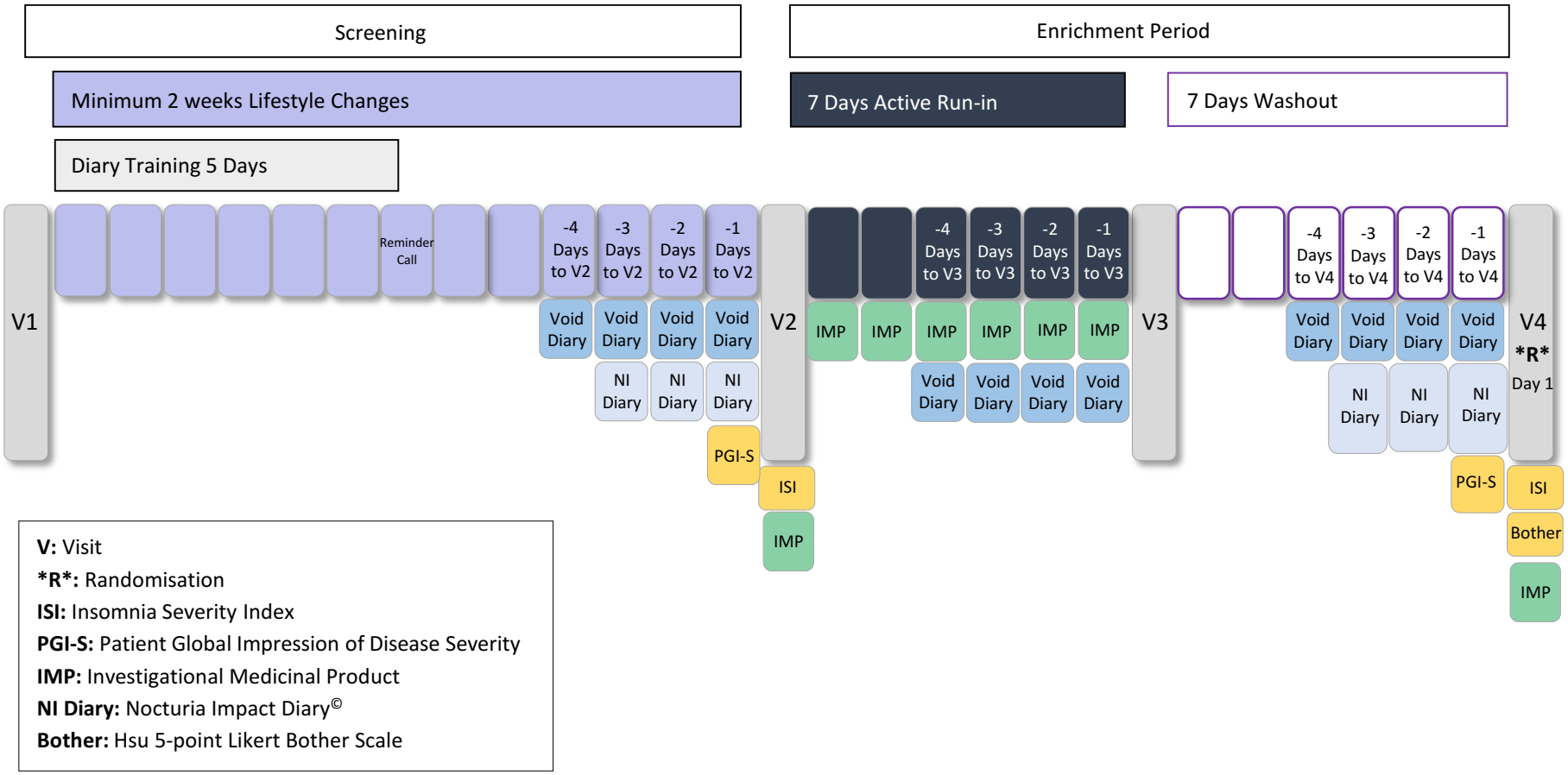


Figure 3-2 e-Diary Assessments and Questionnaires to be Completed by the Subject Prior to Randomisation

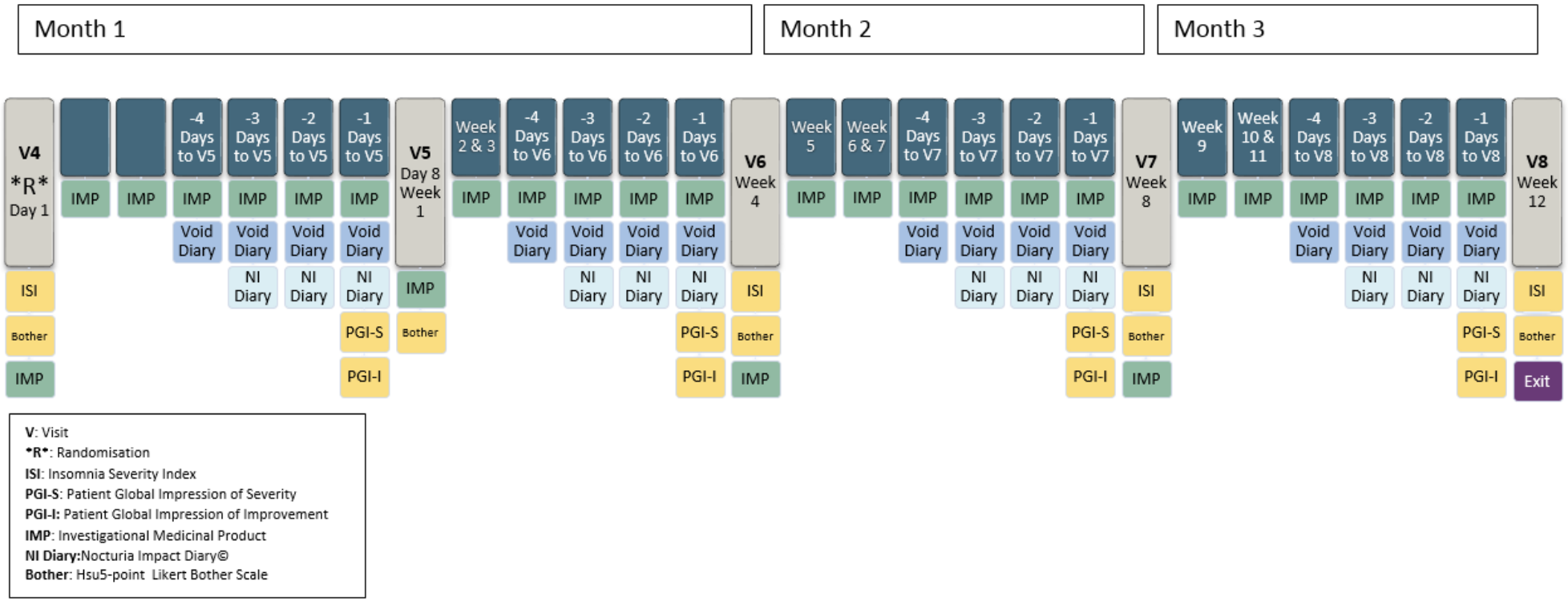


Figure 3-3 e-Diary Assessments and Questionnaires to be Completed by the Subject During the Randomised Treatment Period

3.1.2 Overall Design and Control Methods

This is a randomised, double-blind, placebo-controlled, response-adaptive, dose-finding trial investigating the efficacy, safety and tolerability of 6 different oral doses (50-500 µg) of FE 201836, with desmopressin as a benchmark, during 12 weeks of treatment for nocturia due to NP in adults.

The trial will comprise 8 visits (Section 3.1.1) to the clinic and will consist of a 2-week screening/lifestyle changes period where no IMP will be given, an enrichment period consisting of a 1-week single-blind (to subjects) active run-in period and a 1-week washout period, and a 12-week double-blind randomised treatment period for each subject (Figure 3-1). During the active run-in period the trial subjects will receive 500 µg FE 201836 and placebo to assess safety and establish that subjects who respond to treatment with FE 201836 are included in the trial (i.e., an enrichment design).

The 12-week double-blind randomised treatment period of the trial will follow a response-adaptive Bayesian top-down design. Initially subjects will be randomised to: placebo, 500 µg FE 201836 or desmopressin (for benchmarking only). When approximately 125 subjects have been randomised to the trial, an interim analysis will be conducted to investigate the efficacy of 500 µg FE 201836. If 500 µg FE 201836 is not sufficiently efficacious compared to placebo the trial will be stopped for futility. If 500 µg FE 201836 is efficacious additional doses of FE 201836 (doses 50-350 µg) will be opened up for randomisation of new subjects in order to identify the Minimum Effective Dose (MED) and near maximal Effective Dose (ED_{85}). The ED_{85} is the lowest dose that achieves at least 85% of the effect of the maximum dose (500 µg). After the first interim analysis, subsequent interim analyses will take place every 8 weeks to reassess the randomisation allocation probabilities to 50-500 µg FE 201836, based on observed responses at the respective interim locks. For more information regarding the interim analyses, please refer to Section 3.3 and Section 9.11.2.

After the first interim analysis eligible subjects will be randomised to one of 8 treatment groups (Table 5-1). Each subject will be instructed to take the IMP every night at bedtime with the intention to sleep. 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 (Table 5-1).

Subjects will be asked to follow lifestyle changes (e.g., limiting fluid intake) throughout the entire duration of the trial. In addition, subjects will be asked to complete e-Diary assessments (Section 7.1.1) and PRO questionnaires (Section 7.1.1.3) before and after randomisation (Figure 3-2 and Figure 3-3). One objective of the present trial is to further validate the NI Diary. Therefore, 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), to record the subjects' perception of what constitutes a meaningful change in the NI Diary Total Score (Section 10.3.1).

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).

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).

4.1.2 Exclusion Criteria

Any subject meeting one or more of the following exclusion criteria between Visit 1 (screening) through Visit 4 (randomisation) will be considered as a screening failure:

1. Current diagnosis of Obstructive Sleep Apnoea (OSA)
2. Restless Legs Syndrome (RLS)
3. Bladder Outlet Obstruction (BOO) or urine flow <5 mL/s, as confirmed by uroflowmetry upon suspicion during screening prior to Visit 2
4. Urinary incontinence defined as an average of >1 episode/day in the 3-day e-Diary prior to Visit 2 (occasional urge incontinence during daytime or at night on the way to void is not necessarily exclusionary)
5. [c]
6. Any pelvic or lower urinary tract surgery and/or radio therapy or previous pelvic irradiation within the past 6 months prior to Visit 1. Including e.g., transurethral resection for BOO or BPH, hysterectomy or female incontinence procedures
7. Genito-urinary tract pathology that can in the investigator's opinion be responsible for urgency or urinary incontinence e.g., symptomatic or recurrent urinary tract infections, interstitial cystitis, bladder-related pain, chronic pelvic pain syndrome, or stone in the bladder or urethra causing symptoms
8. A history of cancer with the last date of disease activity/prescence of malignancy within the last 12 months prior to Visit 1, except for adequately treated basal cell carcinoma of the skin
9. History of any neurological disease affecting bladder function or muscle strength (e.g., Multiple Sclerosis, Parkinson's, spinal cord injury, spina bifida)
10. Habitual (fluid intake >3L per day) or psychogenic polydipsia
11. Uncontrolled hypertension, as judged by the investigator
12. [a]
13. Uncontrolled diabetes mellitus, as judged by the investigator
14. Central or nephrogenic diabetes insipidus
15. Known history of Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion
16. History of gastric retention
17. Suspicion or evidence of congestive heart failure, (New York Heart Association [NYHA] class II, III, IV)

[c] Original exclusion criterion omitted as per Clinical Trial Protocol Amendment 03 (applicable for all trial sites).

[a] Original exclusion criterion omitted as per Clinical Trial Protocol Amendment 01 (applicable for all trial sites).

18. Hyponatraemia:
    - Serum sodium level <135 mmol/L at Visit 1(re-tested, with results available within 7 days)
    - Serum sodium level <130 mmol/L at Visit 3 (re-tested, with results available within 7 days)
19. Hepatic and/or biliary diseases:
    - Child-Pugh Class A, B, or C

      or
    - Aspartate aminotransferase and/or alanine aminotransferase levels >3x the upper limit of normal range as well as total bilirubin level >2x the upper limit of normal range
20. Known history of hypersensitivity to desmopressin ODT
21. Pregnancy, breastfeeding, or a planning to become pregnant during the period of the trial
22. Known alcohol or substance abuse
23. Work or lifestyle that may interfere with regular night-time sleep e.g., shift workers
24. Any other medical condition, laboratory abnormality, psychiatric condition, mental incapacity, or language barrier that, in the judgment of the investigator, would impair participation in the trial
25. [d]
26. Previous participation in a nocturia, Benign Prostatic Obstruction (BPO), or OAB clinical trial within the past 6 months prior to Visit 1
27. The subject is in a state of dependence of the sponsor, or is directly or indirectly involved in the conduct of this trial as an investigator, sub-investigator, trial coordinator or other trial staff member, or the subject is a first degree family member, significant other or relative residing with one of the above persons involved directly or indirectly with the trial
28. Use of any restricted therapy not in accordance with the protocol
29. Use of any prohibited therapy listed below:
    - Current or former (within 3 months prior to screening) treatment with any other IMP
    - Unstable electrostimulation or behavioural bladder training program less than 3 months prior to screening (stable electrostimulation or behavioural bladder training program started at least 3 months before screening are acceptable)
    - Thiazide diuretics
    - Antiarrhythmic agents
    - V_2-receptor antagonists/agonists (e.g., vaptans/desmopressin, vasopressin)
    - Loperamide

[d] Original exclusion criterion omitted as per Clinical Trial Protocol Amendment 03 (applicable for all trial sites).

- Botulinum toxin (cosmetic non-urological use is acceptable)
- Valproate

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

Subjects who have given written informed consent will receive a unique (site-specific) screening number and be invited to perform a screening visit (Visit 1).

All screening assessments must be completed and evaluated to confirm that all eligibility criteria are met by the subject. A site-specific Screening Log, for recording of details of all subjects screened and confirmation of eligibility or recording of reasons for screening failure, as applicable, must be maintained at the trial site. The screening number, which will be allocated sequentially in the order in which the subjects are screened, must be entered into the Screening Log.

It is permitted to re-screen a subject in this trial in case a subject has been considered a screening failure due to one or more of the following reasons:

- not fulfilling the inclusion criterion number 6 as defined in Clinical Trial Protocol versions 2.0 (>250 mL), 3.0 (>250 mL), or 4.0 (≥250 mL) but had at least 1 single voided volume ≥200 mL prior to Visit 2
- not fulfilling the inclusion criterion of an NI Diary Total Score of ≥10 points (raw score) prior to Visit 2 (inclusion criterion number 8) as defined in Clinical Trial Protocol versions 2.0 and 3.0
- fulfilling the exclusion criterion of a serum triglyceride level >400 mg/dL (exclusion criterion number 12) as defined in Clinical Trial Protocol version 2.0
- fulfilling the exclusion criterion of aspartate aminotransferase and/or alanine aminotransferase levels >2x the upper limit of normal range and a total bilirubin level >1.5 mg/dL (second part of exclusion criterion number 19) as defined in Clinical Trial Protocol version 2.0
- fulfilling exclusion criterion number 3 as defined in Clinical Trial Protocol versions 2.0, 3.0, and 4.0
- fulfilling exclusion criterion number 5 as defined in Clinical Trial Protocol versions 2.0, 3.0, and 4.0
- fulfilling exclusion criterion number 25 as defined in Clinical Trial Protocol versions 2.0, 3.0, and 4.0
- technical issues with the e-Diary device prior to Visit 2

If a subject has failed screening due to any other reason the subject must not be re-screened for participation in the trial at a later time.

4.2.2 Randomisation

A computer-generated randomisation list will be prepared prior to enrolment of the first subject into the trial. The randomisation list will be adjusted during the course of the trial via a response-adaptive randomisation procedure. At least 50% of subjects should be randomised at trial sites in the USA to allow for an optimised validation of the NI Diary. Therefore, a cap of maximum 150 subjects will need to be set for countries other than the USA.

Subject-specific randomisation numbers will be allocated in the order at which the subjects are being randomised into the trial. The subject randomisation number will be recorded in the Screening Log. It is not permitted for a subject to be randomised in the trial twice.

The first 125 subjects will be randomised to treatment in a fixed manner. The allocation ratio is 2:2:1 for placebo, 500 µg FE 201836 and desmopressin. At the first interim analysis, after 125 subjects being randomised, the allocation ratio is 2:7:1 for placebo, active treatment and desmopressin, respectively. Subjects will be randomised to the active treatment groups of FE 201836 in a response-adaptive randomisation manner. A pre-defined algorithm will be used to determine the relative randomisation to each of the FE 201836 groups. Subsequent interim analyses will be conducted every 8 weeks to adjust the adaptive randomisation probabilities. The enrolment of subjects will continue without any stop at the interim analyses. For more information regarding the interim analyses, please refer to Section 3.3 and Section 9.11.

The screening rate will be monitored such that the accrual of randomised subjects does not overshoot the operating characteristics described in Section 9.1, which could potentially result in a loss of statistical power.

4.2.2.1 Randomisation if Maximum Dose is Lowered

The trial has been designed with the option to decrease the maximum dose of FE 201836 from 500 µg to 350 µg if recommended by the DMC (Section 9.11.1). 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 case subjects have already been randomised to the 500 µg FE 201836 treatment group and have not completed the trial, the DMC will recommend whether or not these subjects may be permitted to remain on treatment with 500 µg FE 201836 for the remainder of the trial. Subjects randomised to treatment with 500 µg FE 201836 who prematurely discontinue the trial due to DMC decision (Section 4.4) may be replaced by subjects randomised to treatment with a lower dose of FE 201836.

If the decision to close randomisation to 500 µg FE 201836 is taken prior to the first interim analysis, i.e., when the first 125 subjects have been 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 first interim analysis the dose-response adaptive randomisation will allocate subjects to the remaining 7 open 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).

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

Details of all concomitant medications/therapies and the main reason for the prescription must be recorded in the medical source record and in the Electronic Case Report Form (eCRF) at screening (Visit 1). Any changes (including new therapies) must be recorded at each subsequent visit.

Any therapy for treatment of nocturia or sleep disorders (e.g., guidance for lifestyle changes, pelvic floor muscle training, electrostimulation, biofeedback treatment) that a subject received before trial initiation should be continued without any change throughout the trial period. All subjects must have normal serum sodium (≥135 mmol/L) at screening and serum sodium levels will be monitored throughout the trial as described in Section 6.1 (Table 6-1) and Section 7.1.3.1.

The following medications will be permitted, provided that the subject has been on a stable dose for the 3 months prior to the screening visit (Visit 1) (i.e., treatment has not been initiated or discontinued and there has been no change in dose):

- Sedative/hypnotic medications for sleep disorders
- Selective Serotonin Reuptake Inhibitors (SSRIs): citalopram, duloxetine, venlafaxine, escitalopram, paroxetine, fluoxetine, sertraline
- Chronic use of Non-steroidal Anti-inflammatory Drugs (NSAIDs)
- Chlorpromazine
- Medicines used for treatment of BPH such as alpha-blockers (doxazosin, tamsulosin, terazosin and alfuzosin) and 5-alpha-reductase inhibitors (e.g., dutasteride and finasteride) and phosphodiesterase-5 inhibitors (e.g., tadalafil)
- Medicines used for treatment of OAB such as antimuscarinic therapy (tolterodine, fesoterodine, oxybutynin, darifenacin, hyoscyamine, trospium, solifenacin) and beta-3 adrenergic receptor agonists (mirabegron)
- Sulfonylurea, including chlorpropamide
- Loop diuretics (furosemide, torsemide, ethacrynic acid) and other classes of diuretics (triamterene, chlorthalidone, amiloride, indapamide) are permitted, either as monotherapy or combination therapy if the subject takes the loop diuretic prior to 4 pm (the timing of this treatment regimen must have been in place for at least 1 week prior to the screening visit [Visit 1])
- Systemic corticosteroids
- Carbamazepine
- Lithium
- Opioids
- Lamotrigine
- Tricyclic antidepressants

Additional serum sodium monitoring should be performed as described in Section 7.1.3.1 if treatment with the following medications is initiated or dosing is increased during the trial:

- SSRIs: citalopram, duloxetine, venlafaxine, escitalopram, paroxetine, fluoxetine, sertraline
- Chronic use of NSAIDs
- Chlorpromazine
- Sulfonylurea, including chlorpropamide
- Loop diuretics (furosemide, torsemide, ethacrynic acid) and other classes of diuretics (triamterene, chlorthalidone, amiloride, indapamide)
- Systemic corticosteroids
- Carbamazepine
- Lithium
- Opioids
- Lamotrigine
- Tricyclic antidepressants
- Any other drug that increases the risk of hyponatraemia

4.3.2 Prohibited Therapy

The following medications are prohibited throughout the duration of the trial (exclusion criterion number 29, Section 4.1.2):

- Current or former (within 3 months prior to the screening visit [Visit 1]) treatment with any other IMP
- Unstable electrostimulation or behavioural bladder training program less than 3 months prior to the screening visit (Visit 1) (stable electrostimulation or behavioural bladder training program started at least 3 months prior to the screening visit are acceptable)
- Thiazide diuretics
- Antiarrhythmic agents
- V_2-receptor antagonists/agonists
- Loperamide
- Botulinum toxin (non-urological use is acceptable)
- Valporate

Any new therapy for treatment of nocturia or sleep disorders must not be initiated throughout the duration of the trial.

4.3.3 Lifestyle Changes and Other Restrictions

In order to prevent hyponatraemia and to avoid interference with efficacy assessment of the treatment:

- The fluid intake must be limited to a minimum (to satisfy thirst only) during the time interval of 1 hour before, until 8 hours after administration of IMP
- The subject should empty the bladder before going to bed with the intention to sleep
- The treatment should be interrupted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis) 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

Subjects will be reminded to follow instructions regarding lifestyle changes throughout the duration of the trial.

Subjects participating in the present trial should refrain from donating blood or sperm throughout the trial period.

4.3.4 Contraception

Female subjects of child-bearing potential must be willing and able to use an acceptable effective contraceptive method throughout the trial. Documentation of the method used must be available. A female subject is considered to be of child-bearing potential following menarche and until becoming post-menopauseal, unless permanently sterile. Post-menopausal is defined as amenorrhea of >12 months duration based on the reported date of the last menstrual period.

In the context of this trial, acceptable effective methods include:

- Transdermal patch
- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

Contraceptive measures will not be required for male subjects participating in the trial based on genotoxicity data obtained in animal studies with FE 201836, as detailed in the Investigator's Brochure.

4.4 Withdrawal Criteria

A subject must be withdrawn from the trial in case of:

- Serum sodium level is ≤125 mmol/L at any time point during the trial
- Significant non-compliance with the trial protocol, as judged by the investigator and/or the sponsor
- Other medical or safety reasons, as judged by the investigator and/or the sponsor
- The subject wishes to discontinue for any reason

A subject has the right to withdraw from the trial at any time for any reason, without the need to justify his/her decision. However, the investigator should record the reason for the subject's withdrawal, if possible. The investigator also has the right to withdraw a subject. Since an excessive rate of withdrawals can render the trial devoid of meaning, unnecessary withdrawal of subjects should be avoided.

Every effort should be made to invite subjects withdrawn/discontinued from the trial to an end-of-trial visit (Visit 8) as soon as possible after a decision of withdrawal/discontinuation has been taken. For any discontinuation, the investigator should obtain the required information and document the date and reason for the premature discontinuation in the eCRF.

In case the subject has withdrawn consent, no new data can be recorded in the eCRF. Correction of previous data and/or recording data related to visits/procedures done prior to but made available after withdrawal of consent (e.g., laboratory results) will be allowed unless the subject disapproves it.

If the reason for withdrawal is an adverse event, the specific event or the main laboratory abnormality must be recorded in the eCRF. The investigator should make thorough efforts to document the outcome.

Subjects discontinued from the trial will not be replaced, except for subjects randomised to treatment with 500 µg FE 201836 in case a decision is taken to decrease the maximum dose of FE 201836 from 500 µg to 350 µg (Section 4.2.2.1).

5 TREATMENTS

5.1 Treatments Administered

In order to maintain the treatment blinding each subject will receive 2 medications (double-dummy design), an oral solution and an ODT formulation, during every treatment period of the trial, as outlined in Table 5-1.

During the active run-in period all subjects will receive 500 µg FE 201836 oral solution (and placebo ODT) for 1 week.

After the lifestyle changes/screening, active run-in and washout periods, eligible subjects will be randomised to a treatment group as follows:

- Prior to the first interim analysis, the first 125 subjects will be randomised to the following treatment groups: placebo, desmopressin or 500 µg FE 201836.
- After the first interim analysis, subjects may be randomised to one of 8 treatment groups: placebo, 50 µg FE 201836, 100 µg FE 201836, 150 µg FE 201836, 250 µg FE 201836, 350 µg FE 201836, 500 µg FE 201836 or desmopressin (25 µg for females and 50 µg for males).

After randomisation, the duration of treatment is 12 weeks.

Table 5-1 Treatment during the Trial

Treatment	Investigational Medicinal Product	
	Active Substance	**Placebo**
Active Run-in		
500 µg FE 201836	500 µg FE 201836 oral solution	Placebo ODT
Washout		
-	-	-
Randomised Treatment Period		
Up to First Interim Analysis		
500 µg FE 201836	500 µg FE 201836 oral solution	Placebo ODT
Desmopressin	Desmopressin ODT (25µg for females and 50 µg for males)	Placebo oral solution
Placebo	-	Placebo oral solution and Placebo ODT
After First Interim Analysis		
50 µg FE 201836	50 µg FE 201836 oral solution	Placebo ODT
100 µg FE 201836	100 µg FE 201836 oral solution	Placebo ODT
150 µg FE 201836	150 µg FE 201836 oral solution	Placebo ODT
250 µg FE 201836	250 µg FE 201836 oral solution	Placebo ODT
350 µg FE 201836	350 µg FE 201836 oral solution	Placebo ODT
500 µg FE 201836	500 µg FE 201836 oral solution	Placebo ODT
Desmopressin	Desmopressin ODT (25µg for females and 50 µg for males)	Placebo oral solution
Placebo	-	Placebo oral solution and Placebo ODT

Each subject will be instructed to take the IMP every night at bedtime with the intention to sleep. In addition, as potential food interaction cannot be ruled out at this point in the development of

FE 201836, subjects participating in the present trial will be instructed to wait for a minimum of 2 hours after eating the main evening meal before taking the IMP.

5.2 Characteristics and Source of Supply

All IMP is provided by Ferring Pharmaceuticals A/S and will be handled according to the principles of Good Manufacturing Practice (GMP). Ferring Pharmaceuticals A/S will provide the trial sites with IMP in amounts sufficient for the trial.

5.2.1 Investigational Medicinal Products

The following IMP will be used in the trial:

IMP:	**FE 201836**
Strength:	50, 100, 150, 250, 350 and 500 µg
Formulation:	Oral solution, bottle of 5 mL
Administration method	For oral use
IMP:	**Desmopressin**
Strength:	25 µg and 50 µg
Formulation:	ODT
Administration method:	To be placed under the subject's tongue, without water
IMP:	**Placebo**
Strength:	-
Formulation:	Oral solution, bottle of 5 mL
Administration method:	For oral use
IMP:	**Placebo**
Strength:	-
Formulation:	ODT
Administration method:	To be placed under the subject's tongue, without water

5.3 Packaging and Labelling

Packaging and labelling of the IMP will be performed under the responsibility of the IMP department at Ferring Pharmaceuticals A/S in accordance with GMP and national regulatory requirements.

The IMP will be labelled in a manner that ensures the treatment blinding of the trial is maintained. The active drug and placebo are visually identical.

The label of the IMP will contain one self-adhesive tear-off portion to be affixed to the Drug Dispensing Log maintained at the trial site.

5.4 Conditions for Storage and Use

The investigator will ensure that the IMP is stored under appropriate conditions in a secure location with controlled access. The storage compartment shall be monitored regularly and the temperature shall be documented.

FE 201836 and placebo oral solution must be stored at 2-8°C (36-46°F) before dispensing. After dispensing, the products should be stored at room temperature.

Desmopressin and placebo ODT should be stored at 25°C (77ºF); excursions permitted to 15-30°C (59-86°F). The product should be kept in the original package to be protected from moisture and light. The product should be used immediately upon opening of the individual tablet blister.

The investigator will ensure that the IMP is stored under appropriate conditions in a secure location with controlled access. The storage temperature shall be monitored regularly and documented in accordance with the instructions provided by the sponsor. Deviations in storage temperature must be reported to the sponsor as instructed in the IMP handling instruction.

Returned IMP from the subjects (used/partly used or unused, including empty packaging material) must be stored separately from non-allocated IMP.

The subjects will be instructed to store the IMP in accordance with the above-mentioned conditions.

5.5 Blinding/Unblinding

5.5.1 Blinding

The IMP will be supplied by the sponsor in individually packed containers.

The IMP for the randomised treatment period will be packaged according to a computer-generated randomisation list prepared for all trial sites. The randomisation list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is declared clean and is released to the trial statistician.

5.5.2 Unblinding of Individual Subject Treatment

An emergency unblinding procedure will be available for the investigator and designated personnel at the sponsor through the eCRF. It is the investigator's responsibility to decide whether it is medically necessary to know which IMP the subject receives (i.e., unblinding) to ensure the subject's welfare and safety. Breaking of the blind for individual subjects in emergency situations is only permitted in case of a Suspected Unexpected Serious Adverse Reaction (SUSAR), or in case of an adverse event where the knowledge of the IMP administered is required for medical management of the subject.

As far as the emergency permits, the need to break the blind will be agreed by the investigator and the sponsor. The investigator who unblinds a treatment will use the eCRF and is required to enter a password and must record the reason for unblinding before the treatment code can be broken. It must also be recorded in the eCRF when, and by whom, the code was broken. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding.

If the sponsor needs to unblind a treatment, the eCRF will be used for unblinding. It is a requirement to enter a password and the reason for unblinding before the treatment code can be broken. It must also be recorded in the eCRF when and by whom the code was broken.

It may be necessary to unblind an individual subject's treatment schedule for the purposes of expedited reporting to the authorities and/or Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs)/Research Ethics Boards (REBs). In that situation, every effort should be made to maintain blinding of the sponsor personnel involved in data analysis and interpretation. Other personnel may be unblinded for SUSARs, including trial site personnel as well as personnel acting on behalf of the sponsor.

Information on whether the blind has been broken for any subjects is available in the eCRF and must be collected before the database is declared clean and is released to the trial statistician.

In case the eCRF cannot be accessed, and hence the emergency unblinding cannot be performed within the eCRF system, the investigator should contact Ferring Global Pharmacovigilance using the contact details below:

Global Pharmacovigilance, Ferring Pharmaceuticals A/S

Tel: [redacted]

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

The IMP will be handled by authorised personnel at the trial site according to instructions provided by the sponsor.

The IMP for the active run-in will only be dispensed to subjects who meet the eligibility criteria at Visit 2.

The IMP for the randomised treatment period will only be dispensed to subjects who meet the eligibility criteria at Visit 4 and are randomised into the trial.

The investigator (or his/her designee) will maintain a Drug Dispensing Log detailing the dates and quantities of IMP dispensed to, and used by each subject, as well as the batch number(s).

Each subject should return all unused and used IMP bottles and ODT blister sheets (empty foils) to the trial site. The delegated designee at each trial site will reconcile all used and unused IMP and maintain all IMP (including empty bottles and ODT blister/foils) for drug accountability. The monitor will verify the drug accountability during the trial.

5.6.2 Assessment of Compliance

Treatment compliance will be verified at Visits 3, 5, 6, 7 and 8, by reviewing the used, partly used and unused IMP and/or subject's statements documented in the source documents in case the IMP is lost.

5.7 Return and Destruction of Investigational Medicinal Products

Subjects will be asked to return unused and used IMP bottles and ODT blister sheets. Used and partly used IMP bottles and blisters (foils) will be destroyed at the trial site according to local regulations and standard procedures at the site, after the drug accountability has been verified by

the monitor. Any unused IMP will be returned for destruction, as instructed by the IMP department at Ferring Pharmaceuticals A/S and in accordance with local requirements.

Documentation on destruction will be forwarded to the sponsor.

6 TRIAL PROCEDURES

The investigator is obliged to keep logs of all screened and randomised subjects. Each subject will receive a unique screening number available at each trial site. Prior to, or at Visit 1, all subjects must receive a detailed explanation (verbal and written information) of the trial and must sign an Informed Consent Form (ICF) after having had sufficient time to consider the participation in the trial. No trial-related procedures must be performed on the subject prior to signing the ICF.

6.1 Trial Flow Chart

The overall trial design is shown in Section 3.1. The assessments scheduled for each visit are presented in the flow chart in Section 6.1, listed in Sections 6.2 to 6.7 and further described in Section 7.

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.

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.

6.3 Visit 2 Active Run-in Period

All assessments and procedures to be performed at Visit 2 are listed below.

- The subject will complete the questionnaire (ISI), in the e-Diary (Section 7.1.1.3.2), at the trial site before any consultation with the trial site personnel takes place.
- Inclusion and exclusion criteria will be evaluated.
- Body weight will be measured.
- Vital signs (blood pressure and heart rate) will be measured.
- The subject will be interviewed about any changes in concomitant medication and about any adverse events since the last visit.
- Blood samples will be drawn for assessment of copeptin.
- The subject will be reminded about lifestyle changes (Section 4.3.3).
- Instructions for start and use of IMP will be given.
- IMP will be dispensed to eligible subjects for the 1-week active run-in (Table 5-1).

Prior to Visit 3 the subject will be reminded to complete the e-Diary (Section 7.1.1) for 3 consecutive days prior to the visit. The e-Diary will be reviewed for completeness (via the web-portal) by the trial site personnel.

Four days after the planned start of IMP treatment the subject will be telephoned to follow-up on safety.

6.4 Visit 3 Washout Period

All assessments and procedures to be performed at Visit 3 are listed below.

- Inclusion and exclusion criteria will be evaluated (specifically inclusion criterion number 9, Section 4.1.1).
- Eligible subjects will enter the 1-week Washout-period.
- The subject will be interviewed about any changes in concomitant medication and about any adverse events since the last visit.
- Body weight will be measured.
- Vital signs (blood pressure and heart rate) will be measured.
- A blood sample will be collected for analysis of serum sodium.
- Used IMP bottles, ODT blister sheets and unused IMP will be collected for drug accountability.
- The subject will be reminded about lifestyle changes (Section 4.3.3).

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.

Prior to Visit 4 the subject will be reminded to complete the e-Diary (Section 7.1.1) for 3 consecutive days prior to the visit. The e-Diary will be reviewed for completeness (via the web-portal) by the trial site personnel.

6.5 Visit 4

All assessments/procedures to be performed at Visit 4 are listed below.

- The subject will complete the questionnaires (ISI and Bother), in the e-Diary (Section 7.1.1), at the trial, site before any consultation with the trial site personnel takes place.
- Inclusion and exclusion criteria will be evaluated (specifically inclusion criterion number 10, Section 4.1.1).
- The subject will be interviewed about any changes in concomitant medication and about any adverse events since the last visit.
- A physical examination including body weight, will be performed.
- Vital signs (blood pressure and heart rate) will be measured.
- Blood samples will be drawn for analysis of haematology, clinical chemistry, coagulation factors and copeptin.
- Urine samples will be collected for urinalysis.
- Serum pregnancy test will be performed in all pre- and perimenopausal female subjects.
- Eligible subjects will be randomised to a treatment group (placebo, 500 µg FE 201836 or desmopressin up until the first interim analysis and placebo, 50-500 µg FE 201836 or desmopressin after the first interim analysis).
- The subject will be reminded about lifestyle changes (Section 4.3.3) and to wait for a minimum of 2 hours after eating their evening meal before taking the IMP.
- IMP will be dispensed (Table 5-1).

Prior to Visit 5 the subject will be reminded to complete the e-Diary (Section 7.1.1) for 3 consecutive days prior to the visit. The e-Diary will be reviewed for completeness (via the web-portal) by the trial site personnel.

6.6 Visit 5 to Visit 7

All assessments/procedures to be performed at Visits 5 to 7 are listed below.

- The subject will complete the questionnaires (Bother [Visits 5, 6 and 7] and ISI [Visit 6 and 7]), in the e-Diary (Section 7.1.1), at the trial site before any consultation with the trial site personnel takes place.
- The subject will be interviewed about any changes in concomitant medication and about any adverse events since the last visit.
- Body weight will be measured.
- 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 (Visit 6).
- Urine samples will be collected for urinalysis.
- Used IMP bottles, blister sheets and unused IMP will be collected for drug accountability.
- IMP will be dispensed.
- The subject will be reminded about lifestyle changes (Section 4.3.3) and to wait for a minimum of 2 hours after eating their evening meal before taking the IMP.

Prior to the next visit (Visits 6, 7 and 8) the subject will be reminded to complete the e-Diary (Section 7.1.1) for 3 consecutive days prior to the visit. The e-Diary will be reviewed for completeness (via the web-portal) by the trial site personnel.

6.7 Visit 8 – End-of-Trial Visit

All assessments/procedures to be performed at Visit 8 are listed below.

- The subject will complete the questionnaires (ISI and Bother), in the e-Diary (Section 7.1.1), at the trial, site before any consultation with the trial site personnel takes place.
- The subject will be interviewed about any changes in concomitant medication and about any adverse events since the last visit.
- Physical examination including body weight will be performed.
- 12-lead ECG will be measured.
- Vital signs (blood pressure and heart rate) will be measured.
- Blood samples will be drawn for analysis of haematology, clinical chemistry (including serum sodium), coagulation factors and copeptin.
- Urine samples will be collected for urinalysis.
- Serum pregnancy test will be performed in all pre- and perimenopausal female subjects.
- Used IMP bottles, blister sheets and unused IMP will be collected for drug accountability.

In addition to the above, a sample of subjects (from trial sites in the USA) who have completed the trial, will be invited to participate in an exit interview (Section 10.3.1.2), by telephone, within 14 days of attending the end-of-trial visit (Visit 8) to record the subjects' perception of what constitutes a meaningful change in the NI Diary Total Score.

6.8 Unscheduled Visits

The subject may be called in for additional unscheduled visits due to safety reasons at the discretion of the investigator or the sponsor, unless the subject has withdrawn his/her consent. The subject may also contact the trial site due to safety reasons for an unscheduled visit. The unscheduled visit may include additional collection of blood samples for safety reasons. The unscheduled visit may also include additional assessments deemed necessary by the investigator such as laboratory samples, ECGs, or other procedures which were missed at a previous visit. All unscheduled visits

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

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.

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.

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.

7.1.1.3 Patient Reported Outcomes

The PRO instruments (questionnaires) that will be used in the trial are listed below. They should be completed in the following order:

- At home in the evening (after completion of the NI Diary):
  - Patient Global Impression of Severity (PGI-S)
  - Patient Global Impression of Improvement (PGI-I)
- At the trial site:
  - Insomnia Severity Index (ISI)
  - Bother (Hsu 5-point Likert Bother Scale)

The two PRO questionnaires that will be completed at the trial site (ISI and Hsu 5-point Likert Bother Scale) are recommended to be completed before any other assessments are performed, by the subject in a quiet place without influence from the trial personnel or accompanying family or friends. It is not permitted to help the subject choose an answer or interpret or rephrase questions which the subject does not understand. The subjects should be informed that there are no right or wrong answers and that all of the subjects' responses will remain confidential.

7.1.1.3.1 Patient Global Impression of Severity and Patient Global Impression of Disease Improvement

Patient Global Impression of Disease scales are commonly used measures of symptom severity, treatment response and the efficacy of treatments (Yalcin, 2003). The PGI-I and PGI-S will be included in the trial to indicate change or stability in global health status for anchor-based analyses to identify thresholds for clinically important changes in, e.g., NI Diary scores and number of nocturnal voids, as described in a separate Psychometric Analysis Plan (PAP). Moreover, both scales will be analysed for treatment effect, as described in Section 9.7.3. To better reflect the current condition, the revised and patient-tested versions of PGI-I and PGI-S will refer to 'night-time voiding', as compared to 'LUTS' (Viktrup, 2012).

The PGI-S is a prospective measure that measures a patient's current severity reported as "None," "Mild," "Moderate," or "Severe" (coded as 1-4). Scores on this measure will provide a patient-rated summary of the severity of the patient's nocturia symptoms.

The PGI-I is a retrospective measure. It will provide a patient-rated summary of change in nocturia since the start of trial treatment, reported as "Very much better," "Much better," "A little better," "No change," "A little worse," "Much worse," or "Very much worse," (coded as 1-7).

PGI-S followed by PGI-I will be completed by the subjects at home in the evening immediately after completing the NI Diary, as outlined in Figure 3-2 and Figure 3-3.

7.1.1.3.2 Insomnia Severity Index

Chronic disruptions of sleep will have consequences for daytime performance and well-being. Nocturia patients often report excessive daytime sleepiness, with some experiencing more severe symptoms, including increased rates of mood disorders and decrease of physical health. Fatigue is a

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.

7.1.2 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.

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.

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.

7.1.3.3 Copeptin

Blood samples for exploratory analysis of copeptin levels in plasma will be collected at Visit 2, Visit 4 and Visit 8. The biomarker copeptin can be easily tested for, and is therefore used as an AVP surrogate to potentially identify low nocturnal vasopressin levels in plasma. In patients with NP, an inverse circadian rhythm of vasopressin is suspected, resulting in low nocturnal concentrations, which may be the root cause of NP. Copeptin may be a useful biomarker to diagnose NP due to low levels of endogenous AVP, thereby identifying the ideal candidate for antidiuretic therapy (Brunell, 2016) and consequently treatment with FE 201836.

7.1.4 Vital Signs

Diastolic and systolic blood pressure (mm Hg) and heart rate (beats per minute) will be measured after resting for 5 minutes in a sitting position, according to usual clinical practice at all trial visits.

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.

7.1.5 24-Hour Urine Volume and Nocturnal Urine Volume

Data on 24-hour urine volume, i.e., including NUV, will be obtained from the 3-day voiding diary (Section 7.1.1.1) completed prior to Visits 2, 4, 5 and 8. In addition, NUV data will be obtained from the 3-day voiding diary completed prior to Visit 3 (Table 7-1).

7.2 Other Assessments

7.2.1 Demographics

Demographic data, including date of birth and race, will be collected at screening (Visit 1).

7.2.2 Medical History

Information on clinically significant previous and concomitant illnesses, signs or findings from assessments and examinations during the screening, including surgical history, will be recorded as medical history at the screening visit (Visit 1).

7.2.3 Concomitant Medication

Information on concomitant medications will be collected at each visit throughout the trial, as described in Section 4.3.1. Concomitant medications are defined as any medication, other than the IMP, taken by the subject at entry and during the trial. Prohibited medications/therapies are listed in Section 4.3.2.

7.2.4 Body Weight and Height

Body weight and height will be measured to calculate the body mass index (BMI). The eCRF will be configured to automatically calculate the BMI. Height (without shoes) will be measured at screening (Visit 1).

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).

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

- 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.

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

8.3 Adverse Events of Special Interest

Hyponatraemia

Serum sodium levels will be monitored throughout the trial as hyponatraemia is a well-known ADR associated with desmopressin treatment (Section 7.1.3.1) and may potentially be associated with FE 201836 treatment. Serum sodium levels should be tested in subjects presenting with signs or symptoms of hyponatraemia. 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.

All cases of serum sodium values ≤125 mmol/L are considered important medical events and must be reported as SAEs, as described in Section 8.5.2.

8.4 Pregnancy and Pregnancy Outcome

If a pregnancy occurs, the IMP should be immediately stopped for the pregnant subject and Global Pharmacovigilance at Ferring Pharmaceuticals A/S must be informed. The pregnancy should be reported via the pregnancy Report Form included in the eCRF system. In case the eCRF cannot be accessed and hence the Pregnancy Report Form cannot be filled in within the eCRF system, a paper Pregnancy Report Form available in the investigator's file should be used and sent to Ferring Global Pharmacovigilance. Contact details to Ferring Global Pharmacovigilance are provided in Section 8.5.2.

A pregnant participant or the partner of a male participant should be followed until termination or until term to ensure absence of congenital anomaly or birth defect that may have resulted from maternal exposure or transmission of the study drug via semen following paternal exposure. The pregnancy should be followed-up at least until the birth of the infant and 4-6 weeks after the birth of the infant. In general, the follow-up will include the course; duration and the outcome of the pregnancy as well as neonatal health.

If a pregnancy results in an abnormal outcome (birth defect/congenital anomaly) this must be reported as an SAE to Global Pharmacovigilance at Ferring Pharmaceuticals A/S.

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.

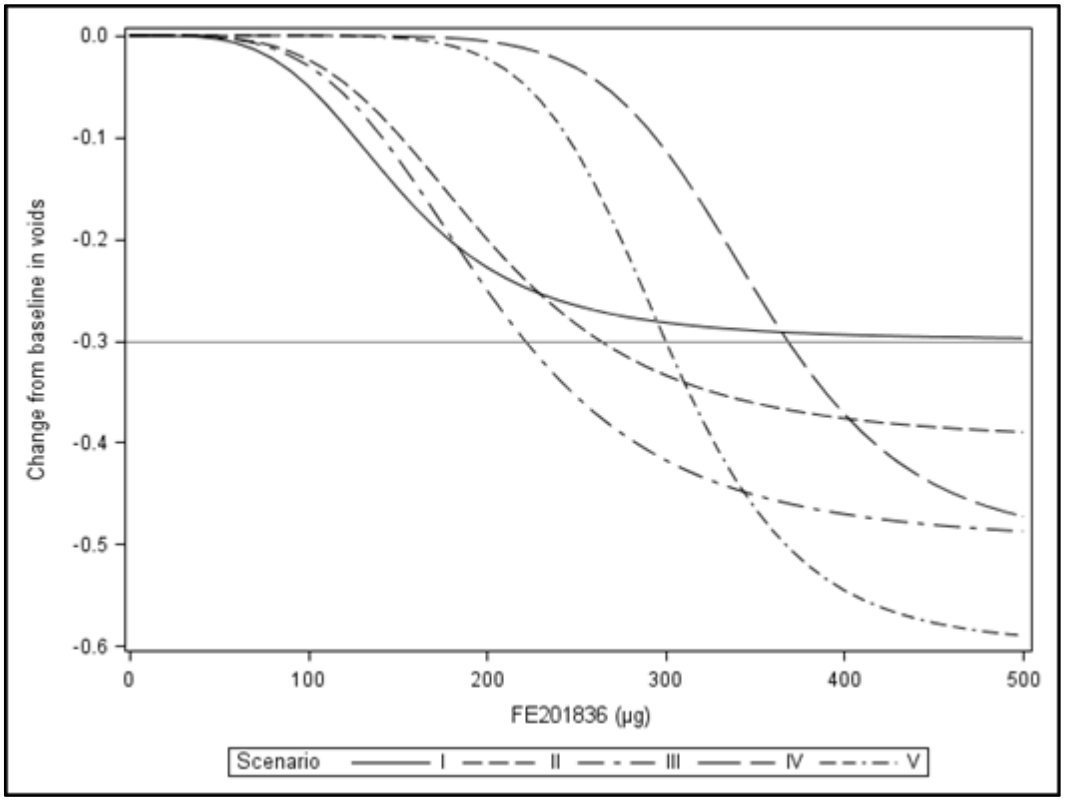


Figure 9-1 Dose-Response Scenarios

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.

Table 9-1 Operating Characteristics

Dose-Response Scenario	Maximum response (α_2)	ED_{50} (α_3)	Average Number of Subjects	Futility Stopping at First Interim	Total Futility stopping	**Power** (Total Success)
Null	0	0 µg	200	75.8%	97.0%	**3.0%**
I	-0.3	150 µg	277	15.7%	47.9%	52.1%
II	-0.4	200 µg	288	7.9%	25.1%	74.9%
III	-0.5	200 µg	296	2.8%	9.6%	**90.4%**
IV	-0.5	350 µg	295	3.4%	15.4%	**84.6%**
V	-0.6	300 µg	298	1.4%	2.7%	97.3%

For each dose-response scenario, 1,000 trials were simulated in order to estimate the operating characteristics presented in Table 9-1. The simulations under the null-hypothesis (no effect) demonstrate that assuming a maximum reduction versus placebo of 0.5 voids, the power (probability of success) reaches approximately 85 to 90%, while the probability of making a false positive conclusion is 3.0%.

9.2 Protocol Deviations

Protocol deviations will be rated as either minor or major. Protocol deviations deemed to impact the primary endpoint and possibly affect the conclusions of the trial will be rated as major. Major protocol deviations will lead to exclusion of data from the Per Protocol (PP) analysis set (Section 9.3.5). Data up to the point where the violation occurs will be used in the evaluations.

Major protocol deviations include, but are not restricted to, the following:

- <2 nocturnal voids (average over 3 diaries) prior to Visit 2 or Visit 4
- NPi ≤33% prior to Visit 2
- <20% decrease in nocturnal diuresis rate (mL/min) from during active run-in (Visit 2 to Visit 3)
- Maximum voided volume <200 mL prior to Visit 2
- Actual treatment not in accordance with randomised treatment
- Significant non-compliant treatment administration and e-Diary completion

Serious unforeseen deviations deemed to impact the primary endpoint of the trial may additionally be rated as major protocol deviations by the sponsor on the basis of a blinded review of data before declaration of clean-file and lock of database. The list of major protocol deviations will be detailed and documented in the clean file document prior to database release to the trial statistician.

9.3 Analysis Sets

9.3.1 Intention-to-Treat Analysis Set for the Enrichment (ITT-ENR) Period

The Intention-to-Treat analysis set for the enrichment period (ITT-ENR) will be comprised of all subjects found to be eligible to enter the enrichment period (1 week active run-in and 1 week washout) at Visit 2. All analyses will be conducted with respect to the planned treatment allocation.

9.3.2 Safety Analysis Set for the Enrichment Period

The safety analysis set for the enrichment period will be comprised of all subjects who received at least one dose of IMP after Visit 2 i.e., during the 1 week active run-in and 1 week washout. The safety analysis set also includes any subject who was found not eligible at Visit 2, but who had at least one administration of IMP after Visit 2. All analyses will be with respect to actual treatment received.

9.3.3 Intention-to-Treat (ITT) Analysis Set for the Randomised Treatment Period

The Intention-to-Treat (ITT) analysis set for the randomised treatment period will be comprised of all subjects randomised at Visit 4. All analyses will be conducted with respect to the planned treatment allocation.

9.3.4 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will be comprised of all subjects in the ITT analysis set with at least one post-baseline record of the number of nocturnal voids (primary endpoint). All analyses will be conducted with respect to the planned treatment allocation.

9.3.5 Per Protocol (PP) Analysis Set

The PP analysis set will be defined as all subjects included in the FAS except those for whom all data are excluded as a result of major protocol deviations as described in Section 9.2.

9.3.6 Safety Analysis Set for the Randomised Treatment Period

The safety analysis set for the randomised treatment period will be comprised of all subjects who have received at least one dose of IMP (placebo, FE 201836, or desmopressin) and have had at least one safety assessment after randomisation (Visit 4). This also includes any subject who was found not eligible at Visit 4, but who had at least one dose of IMP after Visit 4. All analysis will be conducted with respect to the actual treatment received.

9.4 Subject Disposition

Subject disposition with respect to the number of subjects screened, ITT-ENR and ITT analysis sets (Section 9.3.1 and 9.3.3) will be tabulated by treatment group for all subjects. Reasons for not being randomised at Visit 4 will be categorised and summarised for the ITT-ENR analysis set. Subject disposition, with respect to the number of subjects in the safety analysis sets (Section 9.3.2 and 9.3.6), will be presented separately.

1-Kaplan–Meier (1-KM) plots of time to early discontinuation per treatment group will be displayed for the ITT analysis set and the treatment group difference will be tested using the Log-Rank test. In addition, time to early discontinuation by reason for discontinuation and treatment group will be presented using cumulative incidence functions. All premature discontinuations will be summarised and listed by time of and reason for, discontinuation.

Presentations of subject dispositions will be produced for the overall trial population and by gender.

9.5 Enrichment Period Assessments and Analysis Sets

Descriptive statistics for demographics and other pre-baseline characteristics (e.g., number of nocturnal voids, NPi, serum sodium levels, etc.) obtained at Visit 2 (latest) will be summarised for the ITT-ENR and the safety analysis set defined for the enrichment period. Continuous variables will be presented with number of subjects, mean, standard deviation, median, minimum and maximum. Categorical variables will be presented with number and percentage of subjects within each specific category.

Treatment compliance, efficacy and safety pertaining to the enrichment period (Visits 2 through 4) will be summarised by visit for the ITT-ENR and Safety Analysis Set (as defined for the Enrichment period). Tables will be produced for the overall trial population and by gender. Analyses of hyponatraemia during the enrichment period are further described in Section 9.10.3.

9.6 Trial Population

Descriptive statistics for demographics and other baseline characteristics obtained at Visit 4 (latest) will be summarised for the ITT and safety analysis set as outlined above. All data will be listed per subject for the ITT analysis set. Gender specific tabulations will be provided.

9.6.1 Medical History, Concomitant Medication and Other Safety Evaluations

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The version of MedDRA will be documented. Medical history will be listed by subject and summarised by System Organ Class (SOC) and preferred term.

Prior and concomitant medication will be summarised by Anatomical Therapeutic Chemical Classification System (ATC) classification first level (alphabetically), ATC classification second level (in decreasing order of frequency) and treatment group.

9.7 Endpoint Assessments

9.7.1 General Considerations

Unless stated otherwise the efficacy analysis will be presented for the ITT analysis set.

Continuous variables will be presented with number of subjects, mean, standard deviation, median, inter-quartile range, minimum and maximum. Categorical variables will be presented with number and percentage of subjects within each specific category.

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:

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

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}

The final two quantities are also used to characterise the dose-response curve (as they are calculated for each dose d) and to assign weights for the adaptive dose allocation.

9.7.2.2 Overall Trial Outcome

The overall trial outcome will be presented in terms of the quantities of interest in Table 9-3. Tabulated are also their criteria against which the overall trial success will be judged.

Table 9-3 Overall Trial Criteria

	Quantity of Interest	Criteria		
		At the First Interim Analysis	At Intermediate Interim Analyses	At the Final Analysis
Futility	$\Pr(\mu_{MAX} - \mu_{Plb} < -0.3)$	<10%	<5%	
Success	$\Pr(\mu_{MAX} < \mu_{Plb})$			>97.5%

9.7.2.3 Dose-Response

The dose-response will be characterised by the posterior estimates of the mean dose-response at each dose, μ_d and the mean dose-response contrast versus placebo, their associated 95% credibility intervals and the posterior probability $\Pr(\mu_d < \mu_{Plb})$ will be tabulated. Associated with these, the following (posterior) probabilities will also be tabulated: $\Pr(\mu_d - \mu_{Plb} < -0.3)$, $\Pr(\text{dose } d \text{ is MED})$, $\Pr(\text{dose } d \text{ is } ED_{85})$ and $\Pr(\text{dose d achieves } \mu_{MAX})$.

The mean dose-response will also be presented graphically with its 95% credible interval.

9.7.2.4 Sensitivity Analyses

The following sensitivity analyses will be conducted:

- The primary analysis will be carried out using the PP analysis sets.
- A completer analysis will be run testing the sensitivity of the imputation method applied in the primary analysis.
- The primary analysis using different priors specified in the SAP.
- Repeated measures Analysis of Covariance (ANCOVA) using a Missing Not At Random (MNAR) placebo-based pattern mixture model (Ratitch, 2011).

9.7.2.5 Descriptive Analysis

The raw average and raw average change from baseline at each dose will be tabulated together with 95% confidence intervals. No imputations will be done for this analysis which will be based on the observed cases only.

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 9-4 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.

9.7.3.1 Therapeutic Window

The estimated dose-response curve (left-sided y-axis) will be illustrated together with the (3 month) incidences of serum sodium <130 mmol/L and ≤125 mmol/L (both on right-sided y-axis). The horizontal x-axis will represent the dose range of FE201836. The therapeutic window is defined as the dose range where FE 201836 is deemed efficacious while the incidence of hyponatraemia is acceptable. Corresponding efficacy and safety of desmopressin will be illustrated in a side panel for comparison. Two illustrations will be made, one using the ITT and one using the Safety Analysis Set.

The gender-specific therapeutic windows will also be illustrated similarly.

The therapeutic window of nocturnal volume will be presented similarly.

9.8 Explorative Benchmarking Analysis

The explorative benchmarking analysis will descriptively summarise the changes from baseline and percentage changes from baseline in number of nocturnal voids by all treatment groups, including desmopressin. Tables and figures will be produced as appropriate. This analysis will also be repeated by gender

9.9 Extent of Exposure and Treatment Compliance

Treatment compliance will be summarised by treatment group and visit period for the ITT and safety analysis set.

9.10 Safety

9.10.1 General Considerations

Safety analyses with respect to the enrichment period will be based on the Safety Analysis Set defined for the enrichment period, while analysis with respect to the randomised period will be performed using the safety analysis set.

Safety will be assessed by analysis of adverse events, vital signs, clinical chemistry, haematology, urinalysis and physical examination.

Missing values will be treated as missing, except for causality, intensity, seriousness and outcome of adverse events. A worst-case approach will be used: if causality is missing, the adverse event will be regarded as related to the IMP; if the intensity of an adverse event is missing, the adverse event will be regarded as severe; if seriousness is missing the adverse event will be regarded as serious; if onset date is missing it will be assumed to be the first day of dosing; if outcome is missing and no date of outcome is present the outcome is regarded as 'ongoing'.

Data will be presented in summary tables and listings. Categorical data will be summarised by treatment group using the number and percentage of subjects in each category. For calculation of percentages, the denominator will be the total number of subjects in the respective treatment group

in the safety analysis set. Continuous data will be summarised by treatment group using number of subjects, mean, standard deviation, median, minimum and maximum.

All individual subject data will be listed per subject and treatment as observed including any derived values.

9.10.2 Adverse Events

Adverse events will be summarised overall and tabulated by SOC and preferred term using MedDRA. The version of MedDRA will be documented. The total number of subjects reporting an adverse event, the percentage of subjects (%) with an adverse event and the number of events reported will be presented.

Tables will be prepared for the enrichment period and randomised treatment period as outlined in Table 9-5.

Table 9-5 Tabulations of Adverse Events

	Enrichment Period Enrichment period-emergent Adverse Events (Safety Analysis Set Defined for the Enrichment Period)	**Randomised Period** Treatment-emergent Adverse Events (Safety Analysis Data Set)	Gender-Specific Tabulations
Overview of Adverse Events	X	X	Both
Adverse Events by causality (related/unrelated)	X	X	X
Adverse Events leading to death	X	X	Both
Adverse Events by intensity		X	X
SAEs	X	X	Both
Adverse Events leading to discontinuation	X	X	Both
Adverse Events with an incidence of at least 5% in any treatment group		X	X
Non-serious Adverse Events with an incidence of at least 5% in any treatment group		X	X

9.10.3 Adverse Events of Special Interest: Hyponatraemia Episodes

Observed serum sodium levels and the change from baseline will be tabulated by (planned) visit and treatment group. Similar tables will be produced for both trial periods (enrichment and randomised).

The prevalence of worst-case hyponatraemic episodes, as defined in Table 9-6 will be presented by treatment group and visit for the randomised treatment period.

During the enrichment period (active run-in and washout) hyponatraemic episodes will be presented in the same ranges, but here the definition requires only one observation below the upper limit (≥135 mmol/L) to yield a hyponatraemic episode.

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

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).

The dose-response model will be fitted across all doses, i.e., 0-500 µg, but inference will be made only on the doses that remain open to randomisation e.g., 0-350 µg. That is, the MED and ED_{85} doses and the inferences with regards to proof-of-concept and futility will be limited to the dose range (i.e., with a maximum dose of 350 µg FE 201836).

9.11.2 Interim Efficacy Analyses

The planned interim analyses will be conducted by an internal DMC (Section 3.4) according to a separate DMC charter, which will be established before the first interim analysis. The interim analyses will use unblinded efficacy data to infer whether to stop early for futility or to continue the trial as planned.

At the first interim analysis the trial may be stopped due to futility if there is a low probability (less than 10%) that 500 µg FE 201836 is at least 0.3 voids more efficacious than placebo:

$$\Pr(\mu_{MAX} - \mu_{Plb} < -0.3) < 10\%.$$

Up to the first interim analysis (conducted when 125 subjects have been randomised) the allocation ratio is 2:2:1 for placebo, 500 µg FE 201836 and desmopressin. Should the trial continue, the allocation ratios will be changed to 2:7:1, where all doses of FE 201836 (50-500 µg) are opened for response-adaptive allocation. The randomisation probabilities for each dose of FE 201836 will be proportional to the average of *I*(dose is MED) and *I*(dose is ED_{85}), where *I*(target) is the square root of the probability that "dose is target" scaled by the standard error at that dose.

The remaining interim analyses are planned to occur every 8 weeks as depicted in the decision tree (Figure 9-2).

These interim analyses will re-iterate the (overall) futility criteria at the 5% threshold:

$\Pr(\mu_{MAX} - \mu_{Plb} < -0.3) < 5\%$ (see Table 9-2 for interpretation).

At the final analysis (when all subjects have had their 12-week visit, or discontinued prior to this visit) Proof-of-Concept is established if $\Pr(\mu_{MAX} < \mu_{Plb}) > 97.5\%$.

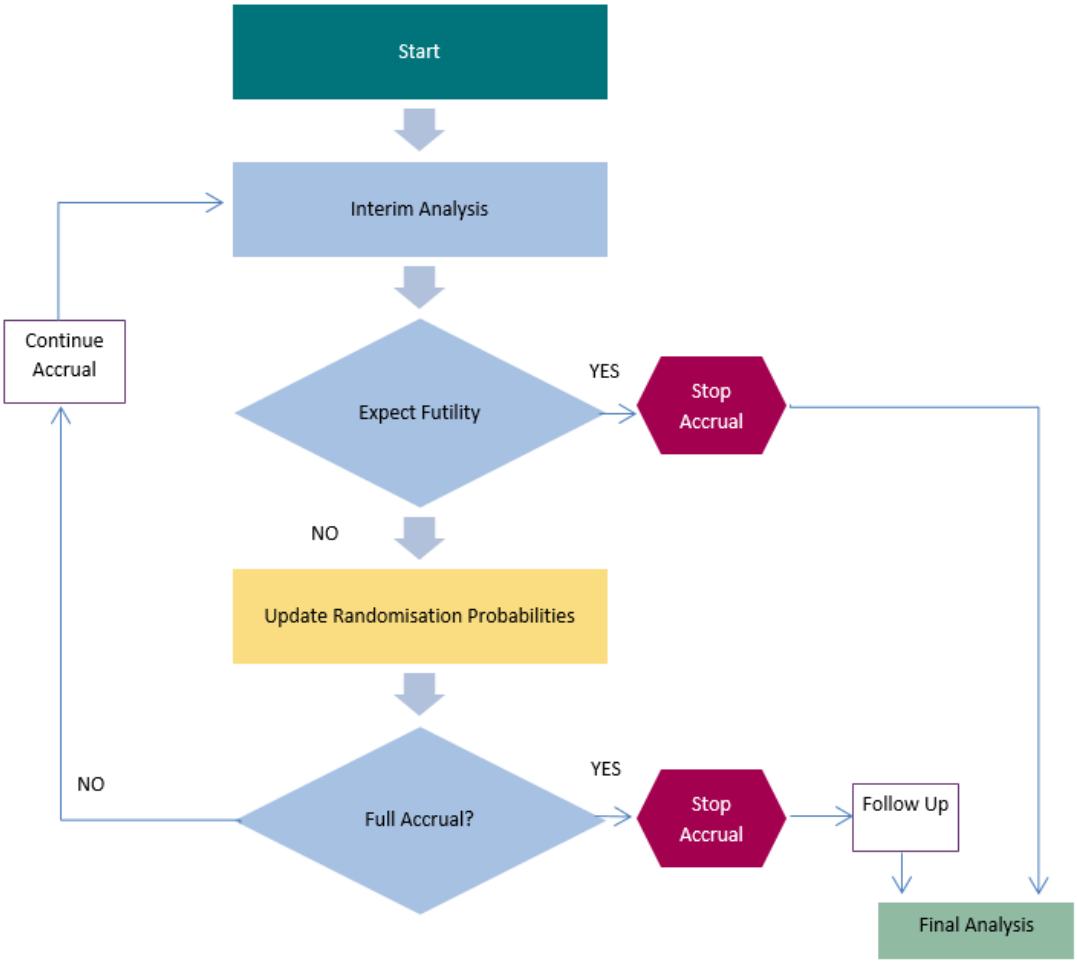


Figure 9-2 Interim Analysis Decision Tree (2nd Interim Analysis and Onwards)

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – International Conference on Harmonisation (ICH) Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents - ICH Definition

Source documents are defined as original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Trial-specific Source Data Requirements - The Sponsor

No specific protocol data can be recorded directly in the e-CRF without a prior written or electronic record. The data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The e-Diary data is part of a process where the subject uses the e-Diary to transmit data to the service provider's database, hence the service provider's database is considered to be the source data. The investigator may need to request previous medical records or transfer records, current medical records must also be available.

For each subject enrolled, the investigator must document in the subject's medical record, that the subject participates in this trial and at least the following information must be recorded:

- Documentation of signed and dated informed consent
- Subject's name and date of birth
- Confirmation of participation in the trial (trial identification, screening/randomisation [subject] number)
- Eligibility of participation in the trial (inclusion/exclusion)
- Relevant medical history
- Nocturia medical history or subject-reported nocturia symptoms
- Visit Dates
- Results of any examinations/tests and assessment performed
- Details of any concomitant medication/therapy

- Details of any adverse events/SAEs (including description and duration)
- Date IMP is dispensed and returned
- Reason for discontinuation/withdrawal, if applicable
- Event of unblinding, including the reason for unblinding, if applicable

The following documents collected during the trial should be stored and archived together with the subject's hospital/medical records or in the investigator file as agreed upon prior to the trial start:

- Laboratory print-outs from central laboratory (and local laboratory, if used) – evaluated, signed and dated by the investigator
- ECG print-outs/reports - evaluated, signed and dated by the investigator
- Subject dispensing logs of IMP
- Relevant records for collection of laboratory samples
- Evaluations of physical examinations
- Demographics

10.2 Electronic Case Report Form

An eCRF system provided by [redacted] an independent third-party Contract Research Organisation (CRO) will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following sponsor and vendor procedures, in accordance with regulatory and system requirements.

Trial data should be entered into the eCRF in a timely manner preferably within 3 working days after the subject visit.

The investigator will approve/authorise the eCRF entries for each subject with an electronic signature which is equivalent to a handwritten signature.

The eCRF system and the database will be hosted at [redacted]. After the trial database is declared clean and released to the statistician, a final copy of the database will be stored at the sponsor. The investigator will also receive a copy of the trial site's final and locked data (including audit trail, electronic signature and queries) as write-protected PDF-files produced by [redacted]. The PDF-files will be stored electronically and will be provided by [redacted] to the investigator before access to the eCRF is revoked.

Entry errors occurring in the eCRF will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction, the name of the person making the correction and the reason for the correction.

10.3 Use of Patient Reported Outcomes

The PRO questionnaires to be used in the trial are described in Section 7.1.1.3.

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].

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.

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, International Conference of Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of eCRF entries compared to source data, verification of drug accountability and compliance to safety reporting instructions.

The investigator will permit the monitor direct access to all source data, including electronic medical records and/or documents in order to facilitate data verification. The investigator will co-operate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the monitor during these visits.

Risk based monitoring will be applied for this trial. The frequency of the on-site monitoring visits will be adapted depending on the risk level of the site and workload. Site risk is based on multiple factors including, but not limited to, the quantity of data generated, quality of the source documents, unreported adverse events or SAEs and number of protocol deviations.

The risk-based monitoring and adaptive monitoring strategy, source data verification process and definition of key variables to be monitored will be described in detail in the Monitoring Plan for the trial.

11.2 Audit and Inspection

The investigator will make all the trial-related source data and records available at any time to quality assurance auditor(s) mandated by the sponsor, or to domestic/foreign regulatory inspectors or representatives from IECs/IRBs/REBs who may audit/inspect the trial.

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2013) and all other relevant regulations.

The subjects must be informed by the investigator and in the Informed Consent Documents that authorised sponsor representatives and representatives from regulatory authorities and IECs/IRBs/REBs may wish to inspect their medical records. During audits/inspections the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/randomisation number will appear on these copies.

The investigator should notify the sponsor without any delay of any inspection by a regulatory authority or IEC/IRB/REB.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the eCRF or any other documents submitted to the sponsor, the subjects will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to the sponsor, e.g., the confidential subject identification code and the signed Informed Consent Documents, will be maintained by the investigator in strict confidence.

11.4 Centralised Statistical Monitoring

Centralised statistical monitoring will be conducted on (but not limited to) the following key aspects of the trial:

- The incidence rate of hyponatraemia throughout the trial
- Key inclusion criteria (number of voids, voided volumes, NI Diary and Bother)
- The number of voids and NI Diary data as collected in the e-Diary throughout the trial
- Monitoring at trial site level will focus on the accumulated trial site data and comparisons across trial sites will be performed

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by the sponsor and agreed upon by the investigator and the sponsor prior to its implementation.

Amendments may be submitted for consideration to the approving IECs/IRBs/REBs and regulatory authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazards to trial subjects may be implemented prior to IECs/IRBs/REBs approval/favourable opinion.

12.2 Deviations from the Protocol

Deviations from the protocol should not occur. If deviations occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. Any deviation must be documented, either as answer to a query in the eCRF, in a protocol deviation report or a combination of both. A log of protocol deviation reports will be maintained by the sponsor. Deviation reports and supporting documentation must be kept in the Investigator's File and in the Trial Master File.

12.3 Premature Trial Termination

Both the investigator (with regard to his/her participation) and the sponsor reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and IECs/IRBs/REBs will be informed.

In addition, the sponsor reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter subjects at an acceptable rate.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by the sponsor and submitted for comments and signature to the signatory investigators.

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the IMP or the trial, including any data and results from the trial will be the exclusive property of the sponsor. The investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to the sponsor.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

At the end of the trial, one or more manuscripts for joint publication may be prepared in collaboration between the investigator(s) offered authorship and the sponsor. In a multi-site trial based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multi-site trials must be reported in entirety in a responsible and coherent manner and results from subsets should not be published in advance or without clear reference to the primary publication of the entire trial.

Authorship is granted based on the International Committee of Medical Journal Editors (ICMJE) criteria (see current official version: *http://www.icmje.org*). The total number of authors is based on the guideline from the relevant journal or congress. In the event of any disagreement in the content of a publication, both the investigator's and the sponsor's opinion will be fairly and sufficiently represented in the publication.

Any external CRO or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

If the investigator wishes to independently publish/present any results from the trial, the draft manuscript/presentation must be submitted in writing to the sponsor for comments prior to submission. Comments will be given within 4 weeks from receipt of the draft manuscript. This statement does not give the sponsor any editorial rights over the content of a publication, other than to restrict the disclosure of the sponsor's intellectual property. If the matter considered for publication is deemed patentable by the sponsor, scientific publication will not be allowed until after a filed patent application is published. Under such conditions the publication will be modified or delayed at the investigator's discretion, to allow sufficient time for the sponsor to seek patent protection of the invention.

13.3.2 Public Disclosure Policy

ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of the sponsor to register the trial in an appropriate public registry, i.e. *www.ClinicalTrials.gov*; a website maintained by the National Library of Medicine (NLM) at the U.S. National Institutes of Health (NIH). The trial will also be made publicly available at the European Union (EU) Clinical Trials Register at *www.clinicaltrialsregister.eu*. Trial registration may occur in other registries in accordance with local regulatory requirements. A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Independent Ethics Committee / Institutional Review Board / Research Ethics Board

An IEC/IRB/REB will review the protocol and any amendments and advertisements used for recruitment. The IEC/IRB/REB will review the subject information sheet and the ICF, their updates (if any) and any written materials given to the subjects. A list of all IECs/IRBs/REBs to which the protocol has been submitted and the name of the committee chairmen will be included in the clinical trial report.

14.2 Regulatory Authorities Approval

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a subject is exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-Trial and End-of-Trial Notification

The end of this trial is defined as the date of the last visit (Visit 8) of the last subject undergoing the trial. An end-of-trial declaration will be prepared when the trial has ended and will be submitted to the IECs/IRBs/REBs and regulatory authorities.

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2013), in compliance with the approved protocol, ICH-GCP and applicable regulatory requirements.

14.5 Subject Information and Consent

The investigator (or the person delegated by the investigator) will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, sources of funding, any possible conflicts of interest, anticipated benefits, potential risks of the trial and the discomfort it may entail, post-trial provisions and any other aspects of the trial which are relevant to the subject's decision to participate. The trial subject must be given ample time to consider participation in the trial, before the consent is obtained. The Informed Consent Documents must be signed and dated by the subject and the investigator who has provided information to the subject regarding the trial before the subject is exposed to any trial-related procedure, including screening tests for eligibility. Subjects must be given the option of being informed about the general outcome and the results of the trial.

The investigator (or the person delegated by the investigator) will explain that the subject is completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for his/her further care and without the need to justify his/her decision.

The subject will receive a copy of the subject information and his/her signed ICF.

If new information becomes available that may be relevant to the trial subject's willingness to continue participation in the trial, a new subject information and ICF will be forwarded to the IECs/IRBs/REBs (and regulatory authorities, if required). The trial subjects will be informed about this new information and re-consent will be obtained.

Each subject will be informed that the monitor(s), quality assurance auditor(s) mandated by the sponsor, IRB/IEC/REB representatives or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review his/her source records and data. Data protection will be handled in compliance with national/local regulations.

14.6 Subject Participation Card

The subject will be provided with a Subject Participation Card bearing the following information:

- That he/she is participating in a clinical trial
- That he/she is treated with FE 201836 / Desmopressin / Placebo
- The name and phone number of the investigator
- The name, address and phone number of the sponsor

The subject will be asked to keep the Subject Participation Card in their possession at all times during the trial and to return it at the last trial visit, if applicable.

Each subject's primary care physician will be notified of their participation in the trial by the investigator, if the subject agrees and if applicable.

14.7 Compliance Reference Documents

The Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2013), the consolidated ICH-GCP, the EU Clinical Trials Directive and other national laws in the countries where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of the sponsor, the monitor and the investigator are defined in the ICH-GCP consolidated guideline and applicable regulatory requirements in the countries where the trial takes place. The investigator is responsible for adhering to the ICH-GCP responsibilities of investigators, for dispensing the IMP in accordance with the approved protocol or an approved amendment and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

Ferring Pharmaceuticals A/S is, as sponsor, responsible for ensuring appropriate general/product liability insurance and, as required in accordance with applicable laws and regulations, country-specific liability insurance coverage for claims made by a trial subject for injury arising from the subject's participation in the trial.

16 ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 15 years after the completion or discontinuation of the trial, if no further instructions are given by the sponsor.

The investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named subject source records and anonymous eCRF data for the sponsor. The investigator must arrange for the retention of this subject identification log and signed informed consent documents for at least 15 years after the completion or discontinuation of the trial.

No trial site document may be destroyed without prior written agreement between the investigator and the sponsor. Should the investigator elect to assign the trial documents to another party, or move them to another location, the sponsor must be notified in advance. If the investigator retires and the documents can no longer be archived by the site, the sponsor can arrange having the Investigator File archived at an external archive.

16.2 Trial Master File

The sponsor will archive the Trial Master File in accordance with ICH-GCP and applicable regulatory requirements.

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18 APPENDICES

Appendix 1

Exit Interview Protocol

Innovative science to capture the patient voice

10 April 2018

Version 7.0

Protocol FENID_001: Phase 2 Evaluation of Patient Reported Outcomes of Nocturia

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Date of Issue:	

CONFIDENTIAL

The information in this document is confidential and will not be disclosed to others without written authorization from Clinical Outcomes Solutions, except for discussions with regulatory authorities or persons participating in the conduct of the study.

Version Number	Summary/Reason for changes	Date Issued
Version 7.0	Removal of the NI Diary criteria listed as "Sub-cluster stratification – NI Diary Total Score of ≥10 points (score 0-44) (Section 4.2.1 Table 2)	10 April 2018
	Removal of "and increased levels of bother and impact) (Section 4.2.1 Table 2)	10 April 2018
Version 6.0	Gift card for participants involvement in the interview will not be an American Express card	16 November 2017

	but rather an electronic gift certificate (updated in section 4.4.1)	
	Change in the NI Diary Total Score to ≥ *10* points (score range 0 –*44*), (Section 4.2.1 Table 2; Cluster	16 November 2017
	Change in wording from "problem" to "condition" to describe nocturia in patient interviews. (Appendix D, Section 2.2)	16 November 2017
	Modified questions 15 and 16 to be consistent with the PGI-I and PGI-S wording that is used in the clinical trial protocol. (Appendix D, Part 4)	16 November 2017

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Abbreviations

CI	Confidence interval
FDA	Food and Drug Administration
HRQOL	Health related quality of life
NI	Nocturia Impact
PGI-I	Patient's Global Impression of Improvement
PGI-S	Patient's Global Impression of Severity
SD	Standard deviation
US	United States

1 Introduction

Ferring Pharmaceuticals is developing FE201836, which is designed to act as a V_2 agonist with an antidiuretic action for the intention to treat nocturia due to nocturnal polyuria in adults. In addition to the frequency of nocturia as a primary endpoint, Ferring wishes to use the Nocturia Impact (NI) Diary as a co-primary endpoint in its registrational studies. The NI Diary is a 12-item, unidimensional 3-day diary of the impact associated with nocturia. As part of the measure validation, the Food and Drug Administration (FDA) Division of Bone, Reproductive, and Urologic Products has requested that subjects are interviewed as they exit the trial to help with understanding what subjects believe is a meaningful change in score. More recently, the FDA have asked that subjects within this study also be asked what constitutes a meaningful reduction in nocturnal voids. This protocol synopsis outlines the study design, sampling characteristics, and methodology for how the exit interviews will be conducted and provides the discussion guide for use with the subjects.

2 Objectives

This is an exit interview study, which will focus on data collection from subjects participating in an ongoing Phase 2 clinical trial of primarily adults in the United States (US) who have nocturia. The main objectives of this study are as follows:

1. Collection of qualitative feedback about the impact of nocturia on a subject's quality of life
2. Assessment of the subject's perception of what constitutes a clinically meaningful change on the NI Diary (Appendix A)
3. Determination of what reduction in nocturnal voids is meaningful to patients (Appendix B)
4. Map the exit interviews back to the clinical trial data to interpret the clinical endpoints

3 Study Methodology

This study is designed to examine the impact of living with nocturia and to assess what a meaningful positive change would be from the patient's perspective in terms of this impact. In exit interviews, patients' 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 the perspective of patients) a meaningful change threshold for indicating positive improvement in the impact of nocturia on a patient's life and, also, meaningful change in nocturnal voids.

This study will include an initial sample of 66 English speaking patients who have been enrolled in a Phase 2 proof of concept FE201836 trial: "A Randomised, Double-blind, Placebo-controlled, Response-adaptive, Dose-finding Trial Investigating the Efficacy, Safety and Tolerability of Oral Doses of FE 201836, with Desmopressin Orally Disintegrating Tablet as a Benchmark, During 12 Weeks of Treatment for Nocturia due to Nocturnal Polyuria in Adults"

To ensure the generalizability of exit interview results, participants will be sampled based on a hierarchical cluster design. Included patients will be proportionate to the clinical trial sample distribution with respect to demographic and clinical characteristics (see Section 4.2 for further details).[1]

Of note: No tests will be conducted as a direct result of this study. No additional visits to a clinical facility will be necessary as part of this study. No identifying information of the patients will be retained by the research team.

4 Study Procedures

4.1 Study Overview

Subjects will be interviewed by telephone within 2-weeks of exiting the trial; those who withdraw early will not be interviewed. Clinical Outcomes Solutions will monitor all subject recruitment via weekly update reports from Quintiles to allow for arrangement with sites to conduct the exit interviews with subjects as they are finishing the trial.

4.2 Sample Size Requirement and Cluster Sampling Design

The primary goal of the exit interview is to estimate meaningful change thresholds for the NI diary within this randomized subject population from the Phase 2 proof-of-concept trial (1:1:1:1:1:1 ratio; FE201836 versus desmopressin versus placebo). For each treatment arm, subjects who demonstrate improvement in the NI Diary scores from Baseline to End of Treatment will be evaluated using a paired-sample t-test. This sample size calculation is based on NI diary parameters and is a mixed methods design (eg, qualitative and quantitative evidence) in which the equivalence of paired means is tested with significance (alpha) set at 0.05, a correlation of 0.40 between assessments, a combined standard deviation of 10 (95% confidence interval [CI] lower bound equal to 10 and upper bound equal to 15), and minimal difference thresholds estimated from previous research of 8.28 and 10.30 point improvement (based on the 0 – 100 transformation). See Table 1 for further details.

Table 1. Sample Size Requirement for Paired t-test of Mean Difference

Mean Improvement Level on the NI Diary Total	Standard Deviation	Actual Power	Sample Requirement per Treatment Arm	Total Subjects
8.28	10	0.807	16 subjects	96 subjects
10.30	10	0.802	11 subjects	66 subjects

Abbreviations: NI = Nocturia Impact

The above power calculation defines the size of the initial set of exit interviews and the *minimum number of subjects* who will be exit interviewed. On the basis of this sample, the change threshold is estimated for defining meaningful change. Next, the robustness of the threshold estimate to increases in sample size using the steps described below is tested). Based on the results, it will be decided whether or not to conduct additional interviews. A "robust" threshold estimate is defined as one that varies < 1 with the addition of the results of additional interviews.

4.2.1 Interview Steps Delineated

- Conduct the initial 66 exit interviews and estimate the threshold for meaningful change based on results for subjects indicating any level of improvement on the NI Diary Total Score.
- Calculate the mean, standard deviation (SD), and 95% CI of the change threshold estimate based on the initial sample size of 66 subjects. If variability in the estimate is greater than the population 10-point standard deviation, an additional 5% of subjects (or 1 subject per treatment arm) will be

interviewed. The threshold will be recalculated to determine if the estimate becomes robust enough to discontinue sampling when the estimate (in whole units) does not change with 2 successive sample size increases (eg, measurement saturation).

- If measurement saturation has been reached, exit interviews will be complete. If not, subjects will continue to be interviewed at an increase of 5% of subjects per treatment arm until measurement saturation is reached.

Please see Table 2 for further details.

Table 2. Cluster Sampling Design Description

Cluster	Listing Unit	Elementary Unit	Application	Methodology for Exit Interviews
Baseline severity (nocturnal voids ≥ 2)	Sites (US and Europe)	Subject: • Sex (50% female) • Age (50% ≥ 65)	• Inclusion of proportionate number of subjects with nocturnal voids ≥ 2 to derive meaningful change thresholds	• Start with 66 subjects and increase the proportion stepwise until measurement saturation is achieved • Measurement saturation will be defined by narrowing of the 95% CIs and an effect size above 0.50 (moderate)

Abbreviations: CI, confidence interval; NI, Nocturia Impact; US, United States

4.3 Subject Recruitment

Recruitment of subjects will be purposive from the Phase 2 trial. Additional information about the trial will be provided to subjects as they are enrolled into the Phase 2 trial. Those that are willing to participate will be provided with an informed consent document to allow full disclosure about the purpose and details of the exit interview.

The clinician at the site will be asked to complete a Case Report Form (Appendix C) that includes specific requirements for subject information to be collected based on the subjects participating in the study (see Table 2 for sub-sample requirements).

4.3.1 Population Characteristics

As described above, subject demographic and medical characteristics will be summarized using the techniques specified for categorical and continuous variables. These variables include:

- Age (≥ 65 and < 65 years)
- Gender
- Baseline nocturnal voids (> 2 and > 3)
- Baseline NI diary scores (mean, SD)

4.4 Interview Process

Clinical Outcomes Solutions scientific staff members will conduct all interviews with participants via telephone to allow the interview to take place as quickly as possible after exiting the trial. Interviews will be conducted in English and will take approximately 45 – 60 minutes to complete. The interview will have four parts:

1. Discussion about experience of living with nocturia and its impacts
2. Discussion about the NI Diary and what constitutes a meaningful change
3. Discussion about change in nocturnal voids and what constitutes a meaningful change
4. Completion of a satisfaction question, overall health status questions, global rating of improvement and, global impression of severity questions

The full discussion guide is provided in Appendix D. Since the discussion guide is complex, mock interviews will be conducted with the interviewers to standardize the way in which it is implemented.

The telephone interviews will be recorded and a copy of the audio-file will be transmitted to a transcription company using 128-bit SSL encryption. Files are only visible to the professionals who have signed strict confidentiality agreements. A random review of transcripts vs. audio-file will be conducted by COS prior to any analysis taking place to ensure accuracy of transcription. Once the transcriptions are approved the transcription company will destroy the audio-files.

4.4.1 Payment

Upon completion of the pre-interview study documents and subject interviews, each subject will be paid $100 via an electronic gift certificate for his/her participation.

5 Analysis

5.1 General Overview

All data processing and analyses for the qualitative interviews will be performed using ATLAS.ti v7.0. For the quantitative analyses, Statistical Analysis Software will be used.

5.2 Qualitative Data

All interview data will be audio-recorded, transcribed, and entered into ATLAS.ti v7.0, a software package which is designed to facilitate the storage, coding, and analysis of qualitative data. This program allows the researcher to code data at different levels of analysis and search for coded data using Boolean operators. The thematic coding scheme will undergo several iterations as the research team codes the preliminary data. Preliminary searches of the coded text will be conducted during and after the initial coding of the data to discover patterns in the data. Initial coded material will be coded into broader core categories and analyzed using thematic analysis. Qualitative data will be analyzed by the outcomes research team executing the study (Clinical Outcomes Solutions) to understand qualitatively what a meaningful change is on the NI Diary.

5.3 Quantitative Data

Data produced from the exit interviews will include improvement in nocturnal voids as well as levels of improvement and severity on items and domains on the NI Diary. Quantitative responses on the prospective and retrospective perceptions of improvement will be included in this evaluation, with the intent to code these responses for triangulation to the clinical trial results. As such, the following variables will be generated from the exit interviews:

- Subject exit interview data at Week 12, including the following:
    - Satisfaction will be evaluated using two methods to understand the distribution of the concept of satisfaction in this population and the relationship with nocturnal void frequency improvement.
        - Comparison of subjects stratified by the absolute response to the "Patient's Global Impression of Improvement" (PGI-I) item.
        - Comparison of subjects who indicated that they are "very satisfied" or "somewhat satisfied" with improvement with those who indicate that they are "somewhat dissatisfied" or "very dissatisfied."
- PGI-I comparison between subjects who indicated that they feel "a great deal better," "much better," or "a little better" to those who indicated that they feel "a little worse," "much worse," or "a great deal worse."
- Patient's Global Impression of Severity (PGI-S comparison between subjects who indicated that they are experiencing "none," "mild," "moderate," and "severe" symptoms).

For perceived improvement in nocturnal voids, subjects will be categorized by change from "no" to "yes" from Baseline to Week 12. For subject interviews, which will be conducted between Weeks 12 and 14, subjects will be categorized by reported improvement as well as satisfaction with improvement in nocturnal void frequency.

5.3.1 Score

The NI Diary Total Score is a raw score valuation ranging between 0 and 44. The current scoring algorithm presents a score transformation from the raw score range to a standardized 0 to 100 scale. Subjects will be presented with the items on the raw score range for this exercise. Within the context of this evaluation, to avoid confusion by the subjects, meaningful change thresholds will be described in raw change score units of -44 to +44 and later transformed to the -100 to +100 by the Ferring statistical programming team.

Nocturnal voids are the subject reported count of getting up during the night to void.

6 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with Good Clinical Practice, including International Conference on Harmonisation Guidelines and consistent with the most recent version of the Declaration of Helsinki. In addition, all applicable local laws and regulatory requirements relevant to the use of therapeutic agents will be adhered to.

The exit interviews will be conducted by experienced staff from Clinical Outcomes Solutions with specific training in conducting qualitative interviews.

If a subject reports an experience that would result in documenting a spontaneously reported adverse event, the study site will use their own standards to document the event. The physician will include the event in the case report form and send it to Clinical Outcomes Solutions within 24 hours.

All COS employees involved in the interviews or analysis of the data will be provided with specific training on reporting of adverse events, which will be provided by Ferring Pharmaceuticals.

7 Confidentiality

All personal study data collected and processed for the purposes of this study will be managed by Clinical Outcomes Solutions with adequate precautions to ensure the confidentiality of the data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

The interviewers will not solicit identifying information that will link any recording to a specific subject. Names will not be transcribed, so the transcripts will remain completely anonymous. If identifying information is inadvertently verbalized during the course of the interview, the Clinical Outcomes Solutions research staff will redact the audio in the transcript. The summary report will not identify subjects by name.

All study-related documentation, including audio recordings, will be held in a secure location during study execution and analysis before being transferred to Ferring's secure servers upon study completion. The audio-recordings will be archived on the COS server after 6-months and will be retained for 7 years.

No information collected during this study will be used outside of the context of the study (ie, commercial purpose) without additional written consent from the subject.

Auditors and other authorized agents of the respective Institutional Review Board, the FDA, COS, and the Sponsor will be granted direct access to the subjects' original interview and other study-related data for verification of study procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. If requested, transcripts will be provided to the site investigator relating only to his or her specific patients.

In any presentations of the results of this study at meetings or in publications, the subjects' identities will remain confidential.

8 Communication and Publication of Results

The sponsor shall retain ownership of all case report forms, data analyses, and reports which result from this study.

All information obtained from the study will be regarded as confidential, until appropriate analysis and review by the sponsor are completed. The results of the study may be published or presented after the review by and in consultation and agreement with the sponsor, and such that confidential or proprietary information is not disclosed.

The Sponsor abides by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research; Authorship and Contributorship statement published by the International Committee of Medical Journal Editors (ICMJE).

9 Financial Disclosure

This study is funded by Ferring Pharmaceuticals.

10 Reference List

(1) Levy, Paul S., and Stanley Lemeshow. Sampling of populations: methods and applications. John Wiley & Sons, 2013.

(2) Hsu A, Nakagawa S, Walter LC, et al. The burden of nocturia among middle-aged and older women. *Obstet Gynecol* 2015; 125:35.

Appendix A. Nocturia Impact Diary

NOCTURIA IMPACT DIARY©

This nocturia (getting up to void at night) diary will assess the daily impact of nocturia on your everyday life. Please answer the questions in the late afternoon or evening and use the scale from 'not at all' to 'a great deal':

Thinking over the day, to what extent....	0) Not at all	1) Slightly	2) Moderately	3) Quite a bit	4) A great deal
1) Was it difficult to concentrate?	0) ____	1) ____	2) ____	3) ____	4) ____
2) Did you feel low in energy and/or tired?	0) ____	1) ____	2) ____	3) ____	4) ____
3) Were you unable to be productive at work or complete your personal, daily activities?	0) ____	1) ____	2) ____	3) ____	4) ____
4) Did you avoid participating in activities that you enjoy?	0) ____	1) ____	2) ____	3) ____	4) ____
5) Did you feel irritable or moody?	0) ____	1) ____	2) ____	3) ____	4) ____
6) Did you limit your fluid intake?	0) ____	1) ____	2) ____	3) ____	4) ____
Thinking about last night, to what extent	0) Not at all	1) Slightly	2) Moderately	3) Quite a bit	4) A great deal
7) Did you lie awake without being able to return to sleep after getting up to use the bathroom at night?	0) ____	1) ____	2) ____	3) ____	4) ____
8) Were you worried about tripping or falling?	0) ____	1) ____	2) ____	3) ____	4) ____
9) Did you feel you got too little sleep?	0) ____	1) ____	2) ____	3) ____	4) ____
Overall, to what extent...	0) Not at all	1) Slightly	2) Moderately	3) Quite a bit	4) A great deal
10) Do you worry that the nocturia will get worse in the future?	0) ____	1) ____	2) ____	3) ____	4) ____
11) Are you concerned with where the bathroom is when away from home overnight?	0) ____	1) ____	2) ____	3) ____	4) ____
12) Does nocturia presently impact your life?	0) ____	1) ____	2) ____	3) ____	4) ____

Appendix B. Nocturnal Voids

Voiding diary

1. Do you have any voiding event to report?
   ☐ YES

   ☐ NO

2. When did the voiding event take place?
   ---------- (format in HH:MM AM/PM)

Appendix C. Case Report Form

Available upon request.

Appendix D. Discussion Guide

SUBJECT DISCUSSION GUIDE

Subject interviews about the impact of nocturia on a subject's health related quality of life and deriving a meaningful change threshold on the Nocturia Impact Diary (NI Diary) and number of nocturnal voids

Interview date: _____ / _____ / _____
MM DD YYYY

Location of interview: _____, _____
City State

Name of interviewer: _____

1 Objectives

The objectives for this study are to explore the impact of nocturia on a subject's health related quality of life (HRQOL). Furthermore, the study aims to assess what a meaningful change is on the Nocturia Impact Diary (Appendix A) and for the number of nocturnal voids.

The interview is divided into the following sections:

- Introduction to the study (5 minutes)
- Part 1: Experience of living with nocturia and its impact on sleep and HRQOL (15 minutes)
- Part 2: Discussion about the NI Diary and meaningful change (25 minutes)
- Part 3: Discussion about nocturnal voiding frequency and what reduction would be meaningful (10 mins)
- Part 4: Rating of change on the patient global assessment of change and patient global impression of severity (5 minutes).

Using the schedule above, the interview should take no more than **1 hour**.

2 Introduction

2.1 Prior to the Interview

Interviewer to review the purpose of the study and confidentiality arrangements, and ask subject's permission to audio record the interview.

- Introduce yourself and state that you work for a research company called Clinical Outcomes Solutions that works closely with pharmaceutical companies to assess how health conditions and treatments impact people's lives.
- Thank the subject for agreeing to participate in the telephone interview.

2.2 Explanation of the Study:

Interviewer to state:

- *The aim of this interview is to find out about your experiences of needing to go to the bathroom at night and how this impacts you. This condition is often referred to as 'nocturia', are you okay with us using the term 'nocturia'?*
    - If the subject is not okay with this, refer to "the need to go to the bathroom at night to urinate" or the subject's preferred reference term.
- *In the first part of the interview I'd like to understand how nocturia affects you and what it is about nocturia that you'd like to see change or improve, for example after taking treatment.*
- *I'll also ask you some specific questions about how often you go to the bathroom at night to urinate and again, I'd like to understand what kind of improvement you'd like to have in terms of how often you go to the bathroom at night.*
- *In the next part of the interview, I'll ask you to look at a short diary questionnaire and talk about how you might respond to the diary to reflect your experiences.*
- *Finally, at the end of the interview I'm going to ask you two other questions. These two questions ask about whether your symptoms have changed and how bad/good they are at the moment.*
- *All of this should take us no longer than 1 hour.*
- *I'll explain all of this again, as we go through the interview but is there anything so far that you have questions about?*
- *Okay, so just to explain, I'm going to audio record the interview to enable me to pay careful attention to what you say and to make certain we accurately capture the information that you provide to me during the interview.*
- *The audio recording will not be shared with the sponsor (ie, the pharmaceutical company). However, a written version of this interview will be prepared that removes any information that would identify you personally.*
- *Please try to speak clearly so that your comments can be heard.*

- *Please don't be afraid to voice any of your opinions. There are no right or wrong answers. If anything isn't clear, please tell me and I will try to explain better, okay?*
- *You may stop the interview at any point you feel the need to, and you may decline to answer any question if you don't feel comfortable.*

Reassure the subject about confidentiality:

- *Your name and contact information will remain with Clinical Outcomes Solutions and will only be accessible to staff members directly involved with this project.*
- *Any information you provide will be reported in a way that protects your privacy by avoiding any mention of your name or other information that could identify you.*
- *The word for word transcript of this interview will be shared with the sponsor of this study (ie, the pharmaceutical company), but your name or any information that identifies you will be removed first.*

2.3 Final Steps

Ask the subject if they have any questions.

Start recording the interview and ask: Do you agree to have this interview audio recorded? Are you ready to begin?

2.4 Important Notes to the Interviewer

Do not lead the subject, we want their open responses. Do probe where appropriate. Cover all the main parts of the interview guide, it is not critical that it flows in the order given, especially if something comes up earlier on in your discussions.

Any medical questions that a subject may raise just explain that you are not a medical professional and that she/he should speak to a physician.

Allow subjects enough time to answer the questions, especially as this is a telephone interview and you cannot observe any non-verbal cues.

3 Discussion Topics

NB: Please remember to allow subjects to respond spontaneously to the following questions, however, do encourage the subject to talk more about the issues that they raise. Probes have been included to help with this but only use when a Subject has not spontaneously mentioned the relevant issue(s).

Some key probes that you can use:

- Tell me more about that?
- How does it make you feel?
- Can you talk more about .....?
- Is it always like this?

Part 1: Experience of living with nocturia and its impact (15 minutes)

Introduction by interviewer: *So in this first part of the interview I'd like to start by asking you about your nocturia and how it impacts your day-to-day life. In particular, I'd like to ask you about how your nocturia affects you now, now that you have completed the clinical trial you have just been part of, and then I'd like you to think back to the time before the clinical trial and tell me how your nocturia affected you then. After that, I'm going to ask you to tell me about any change you may have experienced over the clinical trial.*

Firstly, how long is it since you finished the trial?

1. **Okay thinking about now that you have completed the clinical trial you have just been part of, can you tell me about how your nocturia is, now?**

[Try to focus the subject on discussing the symptoms of nocturia, rather than its impact].

a. What is it like?
b. What physical things do you experience?
c. Thinking about a typical night now (*having completed the trial*), how many times do you typically get up in the night to urinate?

2. **Can you tell me about how your nocturia impacts your life now?**

[Encourage the subject to spontaneously mention the different ways nocturia impacts them. If any of the areas below are not mentioned, then probe specifically on these].

a. Too little sleep?
b. Problems with falling back to sleep?
c. Tiredness?
d. Ability to concentrate?

e. Productivity at work
f. Performing daily activities?
g. Avoidance of activities that you enjoy?
h. Mood?
i. Worry about tripping or falling?
j. Worry about finding a toilet when away from home?
k. Worry about waking others up in the house?
l. Worry about worsening of symptoms?
m. Limited fluid intake?

3. **Now thinking back to the time before the clinical trial you have just completed, can you tell me about your nocturia as it was then?**

[Try to focus the subject on discussing the symptoms of nocturia, rather than its impact].

a. What was it like then?
b. What physical things did you experience?
c. Thinking about a typical night then (*before the trial*), how many times did you typically get up in the night to urinate?

4. **Can you tell me about how your nocturia impacted your life before the clinical trial?**

[Encourage the subject to spontaneously mention the different ways nocturia has impacted them. If any of the areas below are not mentioned, then probe specifically on these].

a. Too little sleep?
b. Problems with falling back to sleep?
c. Tiredness?
d. Ability to concentrate?
e. Productivity at work
f. Daily activities?
g. Avoidance of activities that you enjoy?
h. Mood?
i. Worry about tripping or falling?
j. Worry about finding a toilet when away from home?
k. Worry about waking others up in the house?
l. Worry about worsening of symptoms?
m. Limited fluid intake?

5. **Now thinking about any changes you experienced over the clinical trial, can you tell me how the treatment you received during the clinical trial has affected your nocturia, if at all?**

a. Did your nocturia get <u>better</u> compared to before the trial?
   - When did you notice this getting better? At what point during the trial?
   - How much better did your nocturia get?
   - What did this mean for you?
   - Were you able to do things you weren't able to do before? What things? How?
   - How did this make you feel?

b. Did your nocturia seem to get <u>worse</u> compared to before the trial?
   - When did you notice this getting worse? At what point during the trial?
   - What did this mean for you?
   - How much worse did your nocturia get?
   - Did it stop you from being able to do things in any way? What things? How?
   - How did this make you feel?

c. Did your nocturia stay the <u>same</u>/not change?
   - What did this mean for you?
   - How did this make you feel?

6. **Thinking about just the ways in which your nocturia got <u>better</u> since starting treatment, can you tell me a little more about how this improvement(s) impacted your life?**

[Encourage the subject to spontaneously mention the different ways the improvement in their nocturia has impacted them since the trial. If any of the areas below are not mentioned, then probe specifically on these].

a. More sleep?
b. Less problems with falling back to sleep?
c. Feeling less tired?
d. Greater ability to concentrate?
e. More productive at work?
f. Less impact on daily activities?
g. Less avoidance of activities that you enjoy?
h. Improved mood?
i. Less worry about tripping or falling?
j. Less worry about finding a toilet when away from home?
k. Less worry about waking others up in the house?
l. Less worry about worsening of symptoms?
m. Less need to limit fluid intake?

Were there other positive impacts from taking treatment as part of the clinical trial that we haven't discussed? Tell me about those.

7. [*Only ask this if they mentioned worsening in Q5b*] **Thinking about just the ways in which your nocturia got <u>worse</u> since starting treatment, can you tell me a little more about how it has impacted your life?**

[Encourage the subject to spontaneously mention the different ways the improvement in their nocturia has impacted them since the trial. If any of the areas below are not mentioned, then probe specifically on these].

a. Less sleep?
b. More problems with falling back to sleep?
c. Feeling more tired?
d. Less ability to concentrate?
e. Less productive at work?
f. More impact on daily activities?
g. More avoidance of activities that you enjoy?
h. Impaired mood?
i. More worry about tripping or falling?
j. More worry about finding a toilet when away from home?
k. Less worry about waking others up in the house?
l. Less worry about worsening of symptoms?
m. Less need to limit fluid intake?

Were there any other negative impacts from taking treatment as part of the clinical trial that we haven't discussed? Tell me about those.

Part 2: Discussion about the NI Diary and meaningful change (25 minutes)

<u>Introduction by interviewer:</u> *Okay, so now I'm going to ask you to look at the short diary questionnaire – the Nocturia Impact Diary - you will probably recognize it as you completed it as part of the clinical trial. I'm going to ask you how you might respond to the diary questions based on whether or not your nocturia has changed in any way and what those different scores reflect in terms of your actual experiences.*

Please look at the Nocturia Impact Diary which we have sent you a copy of. Do you have it there?

As you may recall, you completed this diary for the 3 days before each clinical trial site visit. The diary asked you about some of the most common ways that nocturia may impact a person in their day-to-day life. The diary contains 11 questions and one additional global, overall, impact question. Each of the items is scored from 0 to 4 where 0=not at all, 1=slightly, 2=moderately, 3=quite a bit, 4=a great deal. So a higher score is worse because it reflects greater impact. The first 11 questions are added up to make a total score, so this score can range from 0 to 44.

8. **Looking at the diary and the different aspects of life that are affected by nocturia, can you rank order the 11 areas listed in the diary, from most important to least important?**
   a. Taking the first 3 items, ask: What is it about those 3 that make them the most important?
   b. Taking the last 3 items, ask: What makes these the least important?
   c. Are there impacts listed that MUST improve? *INSTRUCTION TO INTERVIEWER: MAKE A NOTE OF HOW MANY IMPACTS THE SUBJECT STATES 'MUST IMPROVE' FOR USE IN Q11 below*
   d. Are there impacts that are not so important to you?

9. **Thinking about [*impact ranked as #1*]:**
   a. What does 'not at all' mean to you?
      - Now what does 'slightly' mean to you?
      - 'moderately'?
      - 'quite a bit'?
      - 'a great deal'?
   b. If you experienced a 1-point reduction (eg, from 'moderately' to 'slightly', or a 'great deal' to 'quite a bit') what would that mean to you?
   c. Would a 1-point change across the categories mean the same?
   d. Is a 1-point reduction in [*impact ranked as #1*] meaningful to you in terms of how you would feel or what you could do?
   e. If no, how many points would you want to reduce [*impact ranked as #1*] by for it to be meaningful to you?
      - How would you feel or what could you do if you experienced this level of reduction?

10. **Repeat Q9 for the impacts stated as 'must improve' in Q8c**

INSTRUCTION TO INTERVIEWER: MAKE A NOTE OF HOW MANY POINTS THE SUBJECT WOULD LIKE TO SEE CHANGE ON EACH 'MUST IMPROVE' IMPACT (PROBES D AND E ABOVE). ADD TOGETHER ALL OF THE RESPONSES TO PROBES D OR E AND USE IN Q11.

11. You want to see improvement on [*number of impacts mentioned in Q8c*] things, and you stated a [THE RANGE OF POINT CHANGES] would be meaningful on each. So, would a [*TOTAL OF RESPONSE TO PROBES D AND E ABOVE*] change be meaningful?

Part 3: Discussion about nocturnal frequency and meaningful change (10 minutes)

Introduction by interviewer: *Okay, so now I'm going to ask you to discuss how often you get up at night to urinate and what sort of change in frequency would be important for you.*

As you may recall, you completed a diary for 3 days before each clinical trial site visit to report how many times you got up at night to urinate. The average number of times you went to the bathroom at night over these 3 days was then worked out (eg, if you had three events the first night, two the 2nd night and one the 3rd night, your average times of going to the bathroom at night to urinate would be two times).

12. As we just discussed, before the clinical trial you got up at night to urinate X times per night on average (see response to Q3c) and at the end of the clinical trial it was X times per night on average (see response to 1c). This means you had a X unit reduction/increase/same.

    Instruction to interviewer: Check that score change is the same as what was discussed during Q5. If there is a reduction go to Q12a–d. If there is not a reduction go to Part 4.

    a. What does it mean for you to go to the bathroom at night, on average, X times less now than before the trial?
    b. Is this an important change for you?
    c. How do you feel because you go to the bathroom at night X times less now?
    d. What are you able to do because of this change in how often you go the bathroom at night?

    Instruction to interviewer: if the change is more than one event, ask about the meaningfulness in one unit reduction and repeat questions a and b above; for example, if the subject had a score change of three, ask them:

    - *Would two less events be meaningful? Why, why not?*
    - *How would you feel or what could you do if you had two less events per night?*
    - *How about one less event, would that still be meaningful? Why, why not?*
    - *How would you feel or what could you do if you had one less event per night?*

Part 4: Rating of change on the patient global assessment of change and patient global impression of severity (5 minutes).

Introduction by interviewer: *So in this final section, I'd like to get your responses to a few other questions that ask you about your overall impression of how your nocturia has been and how it may have changed. I will read the questions and response options to you and ask that you select the response that best reflects your experience.*

13. Overall, how satisfied are you with how the study medication relieved your nocturia?

a. Choose from: "Very satisfied," "Satisfied," "Somewhat satisfied," "Neither satisfied nor dissatisfied," "Dissatisfied," "Somewhat dissatisfied," or "Very dissatisfied"
b. Why did you select that response?
c. What were you thinking about to make you select X?

14. Thinking back over the course of the clinical trial, would you say your overall health status was?

a. Choose from: "Very much improved," "Much improved," "Minimally improved," "No change," "Minimally worse," "Much worse," or "Very much worse"
b. Why did you select that response?
c. What were you thinking about to make you select X?

15. Check the one number that best describes how your night time urination is now **(based on the past 24 hours) (PGI-S)**

a. **None**
b. **Mild**
c. **Moderate**
d. **Severe**

16. Check the one number that best describes how your night time urination is now, compared with how it was before you began taking medication in this study. (PGI-I Revised)

a. **Very much better**
b. **Much better**
c. **A little better**
d. **No change**
e. **A little worse**
f. **Much worse**
g. **Very much worse**

That is the end of the interview today. Do you have any final questions? Thank you so much for taking part today and spending time with me in answering these questions.

Appendix 2

Statistical Design and Operating Characteristics

Trial Code: 000233

Randomized Dose-Response Trial Investigating 6 Different Oral Doses of FE 201836 for the Treatment of Nocturia due to Nocturnal Polyuria in Adults

Prepared for Ferring
By Berry Consultants, LLC
December 16, 2016

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1 Introduction

1.1 Background

This document describes the statistical design of Ferring's randomized dose-response trial investigating 6 different oral doses of FE 201836 for the treatment of nocturia due to nocturnal polyuria in adults. The trial will also include a placebo control arm, and an active comparator arm of desmopressin that will serve as a benchmarking arm. This is a top-down design, meaning that subjects will initially be assigned to the placebo control and the highest dose of FE 201836. After this initial randomization, there will be an interim analysis. If, at that first interim analysis, there is a sufficient probability that the high dose of FE 201836 is effective, the 5 lower doses of FE 201836 will be opened with the objective of characterizing the dose-response curve.

This document describes the features of the simulated design, including the statistical models, decision rules, and simulation scenarios as input into the FACTS (Fixed and Adaptive Clinical Trial Simulator) software. Operating characteristics for the design are also summarized.

1.2 Primary Endpoint

The primary endpoint is the mean change from baseline in the number of nocturnal voids. This is defined as the average change from baseline across measurements taken at 1, 4, 8, and 12 weeks. The average change, inclusive of all measurements, is the final endpoint measurement and therefore the final primary endpoint value will be known at 12 weeks. A lower response indicates fewer voids as compared to baseline and is therefore a subject improvement.

1.3 Treatment Arms

The trial will enroll a maximum of 300 subjects. Subjects will be randomized to potentially one of 8 treatment arms including a control arm, 6 doses FE 201836 and an active comparator. We label these treatment arms as: d = 0 (control), 1, 2, 3, 4, 5, 6 (FE 201836), AC (active comparator). The expected dose levels of FE 201836 are 50, 100, 150, 250, 350, and 500 µg.

2 Statistical Modeling

This section describes the statistical modeling of the primary endpoint. All modeling is Bayesian in nature.

2.1 Final Endpoint Model

Let Y_i be the final primary endpoint value for the ith subject at 12 weeks. We model these outcomes for d = 0,...6 as

$$Y_i \sim N(\mu_d, \sigma^2)$$

where μ_d is the mean response for arm d. The active comparator arm is considered separately. We model the dose-response relationship for d = 0,...,6 using a sigmoidal (E_{max}) model as follows:

$$\mu_d = \alpha_1 + \frac{(\alpha_2 - \alpha_1)\upsilon_d^{\alpha_4}}{\upsilon_d^{\alpha_4} + \alpha_3^{\alpha_4}}$$

where υ_d is the effective dose strength (υ_0 = 0, υ_1 =0.5, υ_2 = 1, υ_3 = 1.5, υ_4 = 2.5, υ_5 = 3.5, υ_6 = 5). The four parameters are interpreted as:

- α_1 is a constant offset, i.e. the response when the effective dose strength is 0.
- α_2 is the maximum response that the model asymptotically approaches as the effective dose strength tends to infinity.
- α_3 is the effective dose strength for the ED50. The ED50 is defined as the dose for which the response is half of the maximum response.
- α_4 is the slope parameter.

These parameters are modeled with prior distributions:

$$\alpha_1 \sim N(-1, 3^2)$$

$$\alpha_2 \sim N(-0.5, 2^2)$$

$$\alpha_3 \sim N^+(2, 2^2)$$

$$\alpha_4 \sim N^+(5, 3.5^2)$$

The error variance is modeled as:

$$\sigma^2 \sim IG(0.5, 0.605)$$

The notation $N^+(\mu, \sigma^2)$ refers to a positively truncated normal distribution. The $IG(a, b)$ is the inverse gamma distribution defined by:

$$f(x|a,b) = \frac{b^a e^{-b/x}}{x^{a+1}\Gamma(a)}$$

2.1 Adjustments in Primary Analysis

The primary analysis applied to actual trial data will be adjusted for the number of baseline voids x_0. This implies that the actual fitted dose-response model for subject i will be

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

The prior distribution for β is modelled as

$$\beta \sim N(0, 10^2)$$

For the purposes of evaluation of trial design and operating characteristics, the model without the adjustment for number of baseline voids will be fitted to simulated trial data.

2.2 Longitudinal Model

The primary endpoint is defined as the average change from baseline across measurements taken at 1, 4, 8, and 12 weeks. As patients complete follow-up visits, we gain knowledge of their final primary endpoint value. First, the change from baseline at an earlier visit is likely correlated with the change from baseline at a later time point. Additionally, as patients complete follow-up visits, we gain partial knowledge of their final primary endpoint value. For example, a patient who has completed 1, 4 and 8 weeks has an average change from baseline through 8 weeks and this value will be highly associated with the primary endpoint yet to be observed that will be inclusive of the last 12 week visit. The trial design makes use of a longitudinal model to allow the unobserved final endpoint value to be imputed from the partial primary endpoint value observed for those subjects that have not yet been observed through the 12-week visit.

Let Y_i be the final endpoint value through the 12 week visit for subject i. Let y_{it} be the intermediate endpoint value at visit t. Longitudinally, y_{it} could be defined in one of two ways. The y_{it} could be defined as the change from baseline to an intermediate visit t. The longitudinal model could be used to impute the y_{it} for all visits and then determine Y_i as the average of all y_{it}. Alternatively, y_{it} could be defined as the

average mean change from baseline inclusive of all measurements obtained through visit t. The last observed y_{it} could be used to impute unknown Y_i.

We consider that the y_{it} follow the latter definition, and are the average mean change from baseline inclusive of all measurements obtained through visit t. We use the last observed y_{it} to impute the final Y_i value for patients who have not yet completed the 12 weeks of follow-up. The dose-response model is then fit on the Y_i values across all enrolled patients. The dose-response modeling is described in Section 2.1. Missing intermediate endpoint values are expected to be rare and will not be imputed. The average at each visit will be computed among only observed completed intermediate visits.

The time course hierarchical model uses the observed average change through visit t to predict the final endpoint value Y_i. The observed average change at the tth visit for the ith subject on dose d is modeled as:

$$y_{it} \sim e^{\gamma_t}(\mu_d + \delta_i) + N(0, \lambda_t^2)$$

The imputed final response (visit T) for the ith subject is modeled as:

$$Y_i \sim \mu_d + \delta_i + N(0, \lambda_T^2)$$

that is, with γ_T equal to 0. Thus, the model has components for

- the per subject difference in response (δ_i) from the mean dose response (μ_d),
- the error as a function of knowing the ith value is modeled, $N(0, \lambda_t^2)$

The prior distributions are:

$$\gamma_t \sim N(\mu_\gamma, \sigma_\gamma^2)$$

$$\delta_i \sim N(0, \tau_i^2)$$

$$\tau_i^2 \sim IG(a_\tau, b_\tau)$$

$$\lambda_t^2 \sim IG(a_\lambda, b_\lambda)$$

We define 3 separate model instance for correlating the averages observed at earlier visits to the final primary endpoint value. The control, active comparator, and 6 active doses of FE 201836 are modeled with separate model instances. Each model instance will be fit using only the data from the arm(s) it corresponds to. All model instances are identical and we use the same priors for all instances. The priors are

$$\tau_t^2 \sim IG(0.5, 0.36125)$$

$$\lambda_t^2 \sim IG(0.5, 0.125)$$

The priors for the longitudinal model parameter γ_t are show in Table 1.

Table 1: Prior parameters for longitudinal model parameter γ_t

	μ_γ	σ_γ^2
Week 1 to Week 12	0	1
Week 4 to Week 12	0	1
Week 8 to Week 12	0	1

2.3 Evaluation of Posterior Estimates

The Bayesian model fitted to the data at each update contains a final endpoint dose-response model and a longitudinal model used for imputing the final mean change from baseline. The posterior distribution for the dose-response parameters is calculated as follows.

1. A longitudinal model is created to link all the visit integrated mean changes from baseline observations to the final integrated mean change over the visits. We label the model as

$$g(y_{it}|\gamma, \delta, \mu, \lambda) \sim e^{\gamma_t}(\mu_d + \delta_i) + N(0, \lambda_t^2)\ t=1,2,3,4$$

2. We created a dose-response model for the inference of the dose-response parameters given the final visit mean integrated change from baseline, y_i (the mean change from baseline of the four visits, which is y_{i4})

$$f(y_i|\alpha, \sigma) \sim \alpha_1 + \frac{(\alpha_2 - \alpha_1)v_{d_i}^{\alpha_4}}{v_{d_i}^{\alpha_4} + \alpha_3^{\alpha_4}} + N(0, \sigma^2)\ \text{ i=1,...,n}$$

The posterior distribution of the dose-response parameters is calculated using Markov chain Monte Carlo simulation. In the algorithm the following steps are taken

A. An observation of the parameters of the longitudinal model $(\gamma, \delta, \mu, \lambda)$ are drawn from their complete conditionals.
B. An observation for the final mean integrated change from baseline for each subject with incomplete data is imputed from $g(y_{it}|\gamma, \delta, \mu, \lambda)$ conditional on the draws from A.
C. An observation from the complete conditional distribution of the parameters

of the dose-response model (α, σ) is drawn given the complete data imputed in B and the naturally completed data in the trial.

D. Any posterior distribution summaries are tabulated from the draws in C that are past the burn-in period of the MCMC algorithm.
E. Repeat A-D for the length of the chain.

Individual parameters are updated by Metropolis Hastings (or Gibbs sampling where possible), using only the y_i and y_{it} data available at the time of the update.

2.4 Quantities of Interest

We define a minimally effective dose (MED), a maximum effective dose, and an 85% effective dose. The minimally effective dose ($MED_{\Delta=-0.3}$) is the smallest dose that achieves at least a difference of $\Delta = -0.3$ relative to control. The maximum effective dose (d_{max}) is the dose with the greatest treatment effect (difference from control). The ED85 is the 85% effective dose, or the smallest dose that achieves at least 85% of the treatment effect (relative to control) achieved by the maximally effective dose, d_{max}. For each dose, d = 1,...6, we calculate the probability it is the $MED_{\Delta=-0.3}$, the d_{max}, and the ED85

We define a number of additional quantities from the posterior distributions that will be used to make decisions during the trial. These include

• the probability that the mean response on dose d is less than on control:

$$\Pr(\mu_d < \mu_0) \text{ for d = 1,...,6}$$

• the probability that the mean response on dose d is less than on control by at least -0.3:

$$\Pr(\mu_d - \mu_0 < -0.3)$$

2.5 Conventions for Missing Data

At any analysis, some subjects may have missing data for the final endpoint. The missing data could result from the subject dropping out of the trial, or because the subject simply has not yet reached the final visit.

If the subject has not yet reached the final visit, but has data from an intermediate visit then the missing endpoint is "imputed" from the longitudinal model. This is described in section 2.2. We impute the final 12-week average change from baseline from the most recently observed average change from baseline at an intermediate visit. Multiple imputation involves sampling, in each MCMC iteration, from the posterior estimate of the subject's final endpoint given their intermediate visit data

and the longitudinal model and the current longitudinal parameters. Thus the imputed value has the uncertainty of the longitudinal model and the estimates of its parameters. If the subject has no interim visit results, the subject's endpoint value is simply imputed from the estimate of the response for the subject's treatment arm (effectively contributing no information to the update of that estimate).

For any subject whose final endpoint is unknown due to drop out, the final outcome will be multiply imputed from the Bayesian model as described above.

3 Trial Design

3.1 Timing of Interim Analyses

The first interim will occur after 125 subjects have enrolled into the trial. This includes 50 subjects to the control (d_0), 50 to the highest dose of FE 201836 (d_6), and 25 subjects on the active comparator (d_{AC}). Subsequent interims will be conducted every 8 weeks and will continue beyond full accrual while the enrolled subjects are completing the 12 weeks of follow-up. Because interims are defined by calendar time, the total number of planned interims, I, is random and will depend on the rate at which subjects accrue to the trial.

3.2 Response Adaptive Randomization

For the initial randomization, 125 subjects will be randomized 4:4:2 to the control, the highest dose of FE 201836 and the active comparator. After this initial randomization, adaptive randomization may begin. During adaptive randomization, subjects will be preferentially allocated to doses most likely to be the MED and ED85. Once adaptive allocation begins, subjects will be randomized in blocks of size 10. Within each block, 2 and 1 subjects will be allocated to control (d_0) and the active comparator (d_{AC}) respectively. The remaining subjects in each block will be allocated adaptively, with allocation probabilities weighted proportional to the probability the dose is the MED and the probability the dose is the ED85. First, we calculate:

$$I_{1,d} = Pr(\text{MED}_{\Delta=-0.3} \text{ relative to control}) \, SE_d^2$$

$$I_{2,d} = Pr(\text{ED}_{85} \text{ relative to control}) \, SE_d^2$$

where SE_d is the standard error of final endpoint data observed at dose d. The randomization probabilities for the adaptively allocated arms will be updated at each interim. They will be weighted according to

$$I_{1,d} + I_{2,d}$$

and the weights will be renormalized to sum to 1.

To avoid assigning subjects to a dose with a minimal chance of being the MED or ED85, any probability less than 0.025 is set to zero at that interim and the resulting probability is reallocated among the remaining doses. In this manner, a dose may be temporarily dropped but may be re-introduced if the adaptive randomization probability increases at subsequent interims.

3.3 Criteria for Stopping Early for Futility

At the first interim analysis with 125 subjects enrolled, the trial may stop for futility if there is a low probability that the maximum effective dose achieves a difference of at least 0.3 from control. Formally if

$$\Pr(\mu_d - \mu_0 < -0.3) < 0.1 \text{ for d = greatest } \Pr(d_{Max})$$

At each subsequent interim analysis, the trial may still stop for futility if there is a low probability that the maximum effective dose achieves a difference of a least 0.3 from control. Formally if

$$\Pr(\mu_d - \mu_0 < -0.3) < 0.05 \text{ for d = greatest } \Pr(d_{Max})$$

If the futility rule is met at an interim analysis, then subject follow up will be discontinued. The final evaluation criteria of trial success will be applied to the currently available data.

3.4 Final Evaluation Criteria

At the final analysis, the trial will be considered successful if the maximum effective dose achieves a significant difference from control,

$$\Pr(\mu_d < \mu_0) > 0.975 \text{ for d = greatest } \Pr(d_{Max})$$

3.5 Design Flow Chart

Figure 1 gives a flow chart depicting the overall structure of the design.

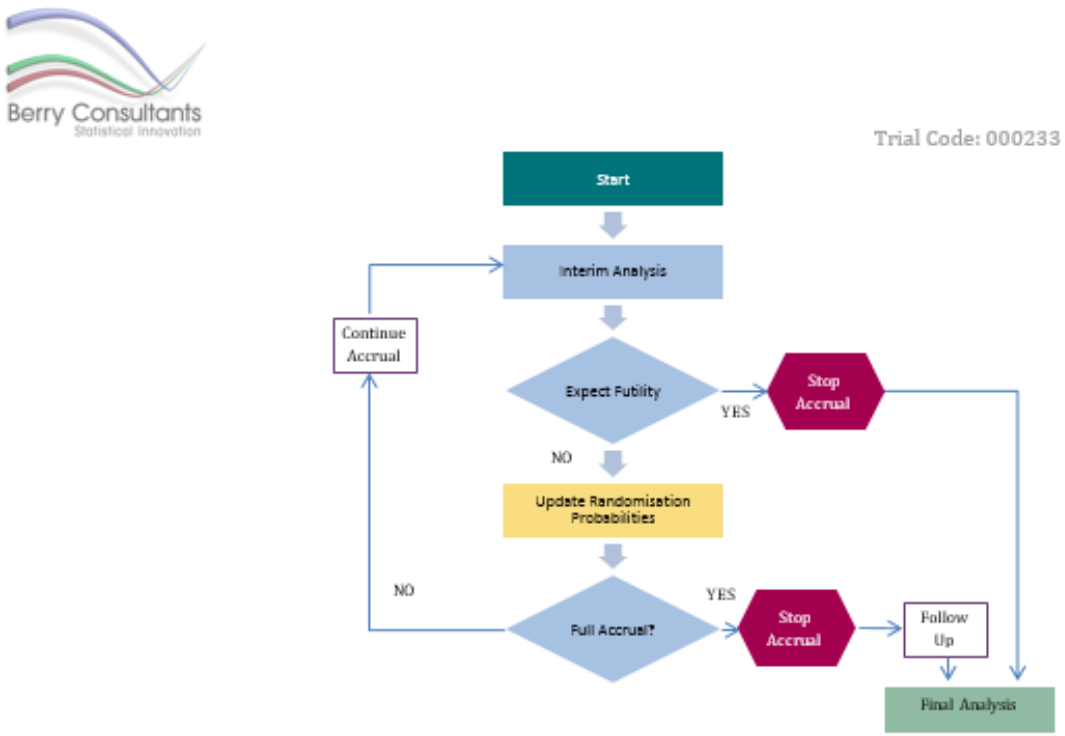

Figure 1: Flow chart of the design

4 Simulation Scenarios

We evaluate the proposed design through trial simulation. We hypothesize several possible underlying truths for the mean response, the longitudinal nature of the data, as well as for trial execution variables such as accrual and dropout. For each of these scenarios, we generate data according to those truths and conduct the trial design as specified above. We repeat this process to create multiple "virtual trials" and we track the behavior of each trial. In this section, we describe the parameters used to generate the virtual subject-level data.

4.1 Virtual Subject Response Profiles

4.1.1 Final Endpoint Scenarios

We consider 6 scenarios for the final 12-week endpoint values. The null model assumes no dose-response. The other 4 scenarios (I-V), depicted in Figure 2, assume a dose-response all based on a sigmoidal model of different size and shape. Table 1 presents the respective parameter values underlying these scenarios. We evaluate these scenarios assuming the standard deviation of the final 12-week endpoint will be 0.95.

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Statistical Innovation

Table 1: Sigmoidal parameter values and their corresponding ED85 and MED of the different scenarios (note: dose runs from 0 to 5 units)

Scenario	α_2 (max effect)	α_3 (ED50)	α_4	ED85	MED
Null	0	-	-	-	-
I	-0.3	150	4	228	-
II	-0.4	200	4	297	263
III	-0.5	200	4	297	221
IV	-0.5	350	8	417	368
V	-0.6	300	8	368	300

Note : α_0=0

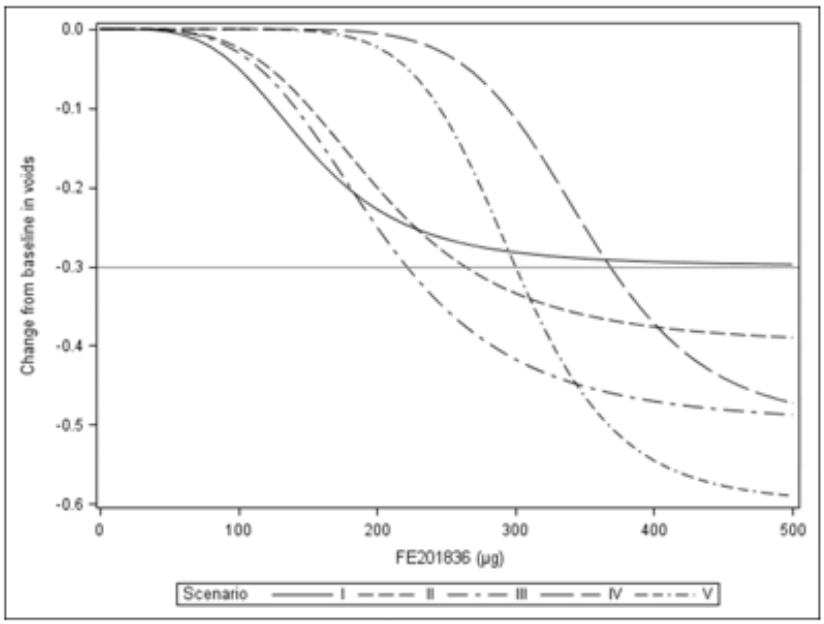

Figure 2: Mean Dose-Response Scenarios

4.1.2 Longitudinal Profile

We define a profile for generating the observed data at each earlier visit. Longitudinal data is simulated through the use of subject specific effects. For the *i*th subject, we simulate a subject effect

$$\delta_i \sim N(0, \tau_d).$$

Then for τ_d (one for each dose d), f_{dt} (one for each dose d and visit t), and ϕ_{dt}, with the constraint that all values are 1 for $t = T$ (the final endpoint time), visits are simulated by computing

$$\kappa_{dt}^2 = \phi_{dt}\sigma_d^2 - f_{dt}^2\tau_d^2$$

and then simulating visits

$$y_{it} \sim N([\theta_d + \delta_i]f_{dt}, \kappa_{dt}^2)$$

The purpose of this structure is to induce correlation through the random effect (interim visits all tend to be higher or lower than the group and arm mean depending on the random effect) while still maintaining a consistent interpretation of the final endpoint variance. Thus, marginally, we find

$$E[y_{it}] = f_{dt}\theta_d$$

and

$$V[y_{it}] = f_{dt}^2\tau_d^2 + \kappa_{dt}^2 = f_{dt}^2\tau_d^2 + \phi_{dt}\sigma_d^2 - f_{dt}^2\tau_d^2 = \phi_{dt}\sigma_d^2$$

so that the f_{dt} terms indicate the proportional value of the mean for the interim visit and the ϕ_{dt} terms indicate the fraction of proportional variance. As these modifiers are constrained to be 1 for the final visit, the interpretation of the final endpoint mean and variance are maintained (and thus the longitudinal model may be turned on and off and produce the same distribution for the final endpoint). We specify the fraction of overall variance that is due to inter-subject variance:

$$\omega_d = \tau_d^2/\sigma_d^2$$

The predictive value of the model occurs due to the correlation between time points, where

$$Corr(y_{it}, y_{it'}) = \frac{f_{dt}f_{dt'}\omega_d}{\sqrt{\phi_{dt}\phi_{dt'}}} \quad [t \neq t']$$

The parameter values for f_t and ϕ_t^2 are shown in Tables 2 and 3. These parameters are based on data observed from previous studies.

Table 2: Response Fraction (f) for the longitudinal profile

Week	f
1	0.8142
4	0.9328
8	0.9874
12	1.0000

Table 3: Fraction of the final variance (ϕ^2) for the longitudinal profile

Week	ϕ^2
1	0.8481
4	0.8329
8	0.8900
12	1.0000

We shall assume that the fraction of the overall variance due to inter-subject variance ω is 0.90

4.2 Accrual Profiles

We simulate the random arrival of subjects into the trial from a Poisson process. We assume accrual will ramp-up linearly for 17 weeks to a peak accrual rate of 8.2 subjects per week.

4.3 Dropout Profiles

We simulate subjects dropping out of the trial. We consider as a scenario in which 15% of subjects on each dose drop out over the course the trial. This is implemented as evenly spaced drop-outs.

5 Operating Characteristics

For the scenarios described above, we simulate 1000 virtual trials and track the behavior of each trial, including the final outcome of the trial, the estimated mean response, etc. The results are summarized across all simulated trials for each scenario.

Table 2 summarizes the trial operating characteristics including the mean sample size, and probabilities of trial success and trial futility. In the null scenario, where the dose-response curve is flat, there is a 3.0% probability of (false-positive) trial success. There is a 75.8% probability that the trial would stop for futility at the first

interim analysis and a total of a 97.0% probability of total futility, cumulative across all the interim analyses (including failure at the final analysis) .

When the highest dose achieves a mean effect of a 0.5 decrease from baseline, there is a ~85 to 90% probability of trial success.

Table 2: Operating Characteristics

Dose-Response Scenario	Maximum response (a_2)	ED50 (a_3)	Average Number of Subjects	Futility stopping at 1st Interim	Total Futility stopping	Power (Total Success)
Null	0	0 µg	200	75.8%	97.0%	3.0%
I	-0.3	150 µg	277	15.7%	47.9%	52.1%
II	-0.4	200 µg	288	7.9%	25.1%	74.9%
III	-0.5	200 µg	296	2.8%	9.6%	90.4%
IV	-0.5	350 µg	295	3.4%	15.4%	84.6%
V	-0.6	300 µg	298	1.4%	2.7%	97.3%

Table 3 shows the probability each dose is selected as the MED. The underlying truth is shown in the last column. Neighboring doses to true MED tend to yield the highest selection probabilities.

Table 4 shows the results for the selection of ED85 and in general the results favor the highest dose due to smoothed curvature leading to not enough effect at lower doses (<15% of maximum effect).

Table 3: Probability each dose is selected as the MED

Table 5: Trial Operating Characteristics – Probability Each Dose is Selected as the MED							
Scenario	50 µg	100 µg	150 µg	250 µg	350 µg	500 µg	**True MED**
N=300							
Null	0.045	0.007	0.001	0.071	0.033	0.843	-
I	0.045	0.047	0.029	0.306	0.057	0.516	-
II	0.024	0.022	0.03	0.372	0.145	0.407	263
III	0.018	0.033	0.043	0.512	0.187	0.207	221
IV	0.008	0.006	0	0.073	0.209	0.704	368
V	0.004	0.004	0	0.19	0.534	0.268	300

Table 4: Probability each dose is selected as ED85

Table 6: Trial Operating Characteristics – Probability Each Dose is Selected as the ED85							
Scenario	50 µg	100 µg	150 µg	250 µg	350 µg	500 µg	True ED85
N=300							
Null	0.761	0.001	0	0.006	0	0.232	-
I	0.19	0.015	0.008	0.131	0.072	0.584	228
II	0.093	0.007	0.005	0.123	0.139	0.633	297
III	0.036	0.001	0.01	0.172	0.223	0.558	297
IV	0.034	0.001	0.001	0.006	0.019	0.939	417
V	0.015	0	0	0.006	0.081	0.898	368