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DESCRIPTION

[0001] Only recently has nocturia been recognized as a clinical entity in its own right as opposed to one of many symptoms comprising various lower urinary tract conditions. It is currently defined by the International Continence Society (ICS) as the complaint that the individual has to wake up at night one or more times to void. This applies to any number of voids at any time during the night provided the person is awake before voiding. (1) In general, the term nocturia refers to urination at night, especially when excessive. It is also referred to as "nycturia."

[0002] There are three broad categories of pathophysiology which account for nocturia: global polyuria; bladder storage problems; and nocturnal polyuria. (2)

[0003] Global polyuria is defined as urine output $> 40\text{ml/kg}$ body weight during a 24 hour period. Causes of polyuria include diabetes mellitus, diabetes insipidus, and primary thirst disorders.

[0004] Bladder storage problems are characterized by frequent voids with small urine volumes. Causes of bladder storage problems include detrusor over activity (neurogenic and non-neurogenic); bladder hypersensitivity; bladder outlet obstruction; primary bladder pathology such as cystitis, calculi and neoplasia; and urogenital aging. A pattern of frequent waking and voiding is also characteristic of a primary sleep disturbance which should be part of the differential diagnosis in the evaluation of a patient with nocturia.

[0005] Nocturnal polyuria is defined as the production of an abnormally large volume of urine during sleep. Healthy young adults from 21-35 years of age excrete approximately $14 \pm 4\%$ of their total urine between the hours of 11 p.m. and 7 a.m. whereas older people excrete an average of $34 \pm 15\%$. (3-4) The ICS currently defines nocturnal polyuria as a nocturnal urine volume greater than 20 - 30% of total 24 hour urine volume, depending on age and in the absence of polyuria. (5)

[0006] Nocturnal polyuria may be secondary to systemic conditions such as congestive heart failure, peripheral edema due to venous stasis or lymphostasis, renal or hepatic failure, lifestyle patterns such as excessive nighttime drinking, and obstructive sleep apnea. Several studies suggest that some individuals with nocturia may have a loss of the normal circadian rhythmicity of arginine vasopressin (AVP) secretion. (6-12) AVP is the hormone primarily responsible for the regulation of urine production. In healthy adults, there is a diurnal release of AVP with peak blood concentrations occurring during the hours of sleep. (13) Blunting of the nocturnal phase of AVP secretion in subjects with nocturia would provide one plausible physiologic explanation for increased nocturnal urine production. However, not all patients with nocturia lack circadian AVP variation, and not all patients lacking circadian AVP variation have nocturia. (14) There are multiple physiologic changes in the mechanisms governing water and sodium regulation which can alter the diurnal rhythm of urine excretion. These include age-related declines in renal concentrating ability and plasma renin concentrations. (15)

[0007] Estimates of nocturia prevalence vary widely depending on the definition used, analytical method employed and population and region surveyed. (16-28) Despite these limitations, the literature strongly indicates that nocturia is a common and bothersome condition in males and females that increases in both prevalence and severity with age.

[0008] One recent large survey, involving more than 19,000 males and females age 18 and older in five countries (Canada, Germany, Italy, Sweden, and the United Kingdom) and utilizing the ICS definition of nocturia (one or more times per night) showed that nocturia was the most prevalent lower urinary tract symptom - reported by 48.6% of men and 54.5% of women - and increased from 34 - 44% in individuals less than 39 years old to over 70% in those aged 60 years or more. Even with a higher threshold of two or more voids per night, the nocturia prevalence of 21 - 24% exceeded that of any other lower urinary tract symptom. (29)

[0009] Older adults often cite nocturia as one of the most bothersome lower urinary tract symptoms. In a community-based survey of 423 men age 40 and older in the UK, 58 (14%) reported nocturia at least twice per night. And 67% of these reported that it was "at least a bit of a problem" - the second most bothersome symptom after frequency at least 9 times per day (92%), and more bothersome even than nocturnal incontinence (60%). (30) A community-based survey conducted in the USA including 720 subjects with nocturia showed that as little as one void per night was not only bothersome, but negatively affected health-related quality of life and sleep. For respondents with nocturia ≥ 2 times per night, the impact on health related quality of life was similar to that of type 2 diabetes and greater than that of hypertension. (31)

[0010] The most pernicious effect of nocturia is not excessive voiding *per se*, but its impact on sleep quality and subsequent daytime function as a consequence of sleep disruption. There is a well established relationship between nocturia and sleep

quality. A community-based Dutch survey of 1485 people age 50 and older reported that 25.3% reported disturbed sleep maintenance, for which nocturia was the most frequent cause (67.5%). (32)

[0011] Asplund and Aberg investigated the relationship between sleep and nocturia in a sample of 3000 women and found that sleep deteriorated in association with increased nighttime voiding. Women with 3 or more voids per night reported four times more often that they lacked sleep and suffered from daytime sleepiness. (33)

[0012] Insufficient sleep and daytime fatigue have been linked with depression, mood alteration and diminished quality of life. (34-36) A community-based Swedish survey of 203 working individuals with nocturia and 80 randomly selected controls showed that the group with nocturia had significantly lower levels of vitality and utility and greater impairment of work and activity as a consequence of sleep deprivation. (37)

[0013] Nocturia is also associated with an increased incidence of falls during the nighttime hours. (38) Falls are a major health problem among older persons and are the leading cause of death from injuries in this age group. (39) In a study evaluating the risk of falls in ambulatory patients 65 years of age and older with nocturia, the odds ratio for falling increased from 1.46 for subjects with one nocturia event to 2.15 for subjects reporting more than three nocturia events per night. (40)

[0014] Vasopressin is the primary physiologic determinant of free water excretion. It increases the water permeability of the luminal membrane of the renal cortical and medullary collecting ducts thereby promoting free water reabsorption and reducing urine production. As nocturia is the clinical consequence of excess nocturnal urine production relative to bladder capacity, reduction of nocturnal urine volume should logically result in fewer nighttime voiding episodes.

[0015] Desmopressin is a synthetic analogue of the naturally occurring hormone 8-arginine vasopressin, with modifications including deamination of 1-cysteine and substitution of L-arginine at position 8 by D-arginine. Desmopressin exhibits a high and specific antidiuretic effect as disclosed in U.S. Patent No. 3,497,491. The resulting molecule has an antidiuretic-to-vasopressor ratio 3000-fold greater than vasopressin and a longer duration of action. (41)

[0016] Due to the bothersome nature and varied symptoms associated with nocturia, further investigation of desmopressin was warranted. Those investigations examined the efficacy and safety of desmopressin in broad populations. The result was surprising gender, age, and dose effects of desmopressin.

[0017] WO2009/143356 discloses the administration of an orodispersible desmopressin formulation to increase the initial period of sleep undisturbed by nocturia.

SUMMARY

[0018] According to the present invention there is provided a composition comprising an orodispersible dose of desmopressin of 25 μ g measured as the free base of desmopressin, for use in reducing nocturnal voids in a female patient in need thereof, wherein the dose is for administration to the patient prior to bedtime and reduces the patient's nocturnal voids compared to before administration, and wherein the mean reduction in nocturnal voids at week 52 of administration is increased compared to the mean reduction in nocturnal voids at day 28 of administration.

[0019] The dose of desmopressin free base may be supplied in the form of the acetate salt of desmopressin.

[0020] The orodispersible dose of desmopressin may be a dosage form comprising desmopressin acetate, gelatin, mannitol and citric acid.

BRIEF DESCRIPTION OF DRAWINGS

[0021]

Figure 1 graphically illustrates the weekly change from baseline in mean number of nocturnal voids along with the corresponding p-values.

Figure 2 graphically illustrates the mean observed and predicted change in nocturnal voids by gender and dose.

Figure 3 graphically illustrates the decrease in total and nocturnal urine volume for the placebo, 10 µg, 25 µg, 50 µg, and 100 µg groups.

Figure 4 graphically illustrates the mean observed and predicted change in nocturnal urine by gender and dose.

DESCRIPTION

[0022] Particular aspects of the disclosure are described in greater detail below. The terms and definitions as used in the present application and as clarified herein are intended to represent the meaning within the present disclosure.

Terms and Definitions

[0023] The singular forms "a," "an," and "the" include plural reference unless the context dictates otherwise.

[0024] The terms "approximately" and "about" mean to be nearly the same as a referenced number or value. As used herein, the terms "approximately" and "about" should be generally understood to encompass $\pm 10\%$ of a specified amount, frequency or value. With regard to specific values, it should be understood that specific values described herein for subject populations (e.g., the subject of the described clinical trial) represent median values, unless otherwise indicated as, e.g., mean values. Accordingly, aspects of the present disclosure requiring a particular value in a subject are substantially supported herein by population data in which the relevant value is assessed to be a meaningful delimitation of the subject population.

[0025] As used herein, the term "first sleep period" refers to the time elapsed from bedtime to either first void or morning arising.

[0026] The term "hyponatraemia" as used herein refers to a serum sodium value below the lower limit of the normal reference range, for example, a serum sodium level <130 mmol/L.

[0027] The term "nocturnal enuresis" as used herein refers to a condition in which a person who has bladder control while awake urinates while asleep.

[0028] As used herein, the term "nocturnal polyuria" refers to an increased nocturnal output of urine. For example, a ratio of nighttime urine volume over the 24-hour urine volume to be equal to or greater than 33%.

[0029] As used herein, the term "nocturnal urine" refers to the total urine volume from 5 minutes after bedtime until rising in the morning, including the first void within 30 minutes of rising.

[0030] The term "nocturnal void" as used herein refers to a void occurring from 5 minutes after bedtime until rising in the morning with the intention of getting up.

[0031] The term "nocturia" refers to the complaint that an individual has to wake up at night one or more times to void.

[0032] The term "overactive bladder" as used herein refers to urgency, with or without urge incontinence, usually accompanied by frequency and nocturia.

[0033] The term "polydipsia" as used herein refers to excessive fluid consumption.

[0034] The term "urine osmolality" as used herein refers to the concentration of electrolytes in urine.

[0035] The term "uroflowmetry" as used herein refers to a measurement of the rate of urine expelled from the bladder during bladder emptying. Flow rate is measured as mL/sec voided.

[0036] The terms "administer," "administration" or "administering" as used herein refer to (1) providing, giving, dosing and/or prescribing by either a health practitioner or his authorized agent or under his direction desmopressin, and (2) putting into, taking or consuming by the patient or person himself or herself, desmopressin.

List of Abbreviations

[0037]

Abbreviations

Meaning of abbreviations in document
AE
Adverse Event
ITT
Intention-To-Treat
LOCF
Last-Observation-Carried-Forward
MED
Minimum Effective Dose
OC
Observed Cases
PP
Per Protocol
SD
Standard Deviation
SAE
Serious Adverse Event
NQoL
Nocturia Quality of Life Questionnaire
PSQI
Pittsburgh Sleep Quality Index
SF
Short Form
µg
Microgram
WebEZ
Web Based Centralized Patient Randomization System

Melt Formulation

[0038] Desmopressin Melt tablets contain desmopressin acetate in a freeze-dried presentation formulated with fish gelatin, mannitol and citric acid. The resulting oral lyophilisate disintegrates instantaneously in the mouth without the need for water. An orodispersible pharmaceutical dosage form of desmopressin with good bioavailability is described in U.S. Patent Application No. 10/513,437 (U.S. Pub. No. 2005/0232997 A1). The Melt dosage form is preferably provided as a desmopressin acetate salt. The desmopressin dosage may be expressed as free base, even though the desmopressin is actually supplied as the acetate salt. Except where otherwise indicated, the doses utilized in the present methods correspond to desmopressin free base even though the dosage form is a desmopressin acetate. Therefore, the 100 µg dose of desmopressin described herein is 100 µg of desmopressin free base, which corresponds to a proportionately higher weight value of desmopressin acetate (approximately 112.4 µg of desmopressin acetate for a desmopressin Melt preparation that is 89% w/w of desmopressin free base and for which the balance of 11% w/w is acetate, water and impurities). Similarly, the 50 µg, 25 µg, and 10 µg dosages all represent the weights of desmopressin free base, with the corresponding weights of desmopressin acetate being proportionately higher. Accordingly, 0.1 mg of desmopressin acetate is equivalent to about 89 µg of desmopressin free base.

[0039] The relative bioavailability between the tablet and melt formulations was investigated in an open-label, randomized crossover study in which 28 healthy subjects were administered 240 µg melt and 0.4 mg tablet (given as 2 x 0.2 mg tablets) separated by seven days. AUC, C_{max}, T_{max} and t_{1/2} were similar, indicating that 0.1 mg tablet results in exposure similar to that of a 60 µg melt (equivalent to 67 µg of desmopressin acetate).

EXAMPLE: Clinical Study (the example includes comparative data not forming part of the claimed invention)**Objectives**

[0040] The primary objectives of Part I of this study (28-day efficacy) were: (1) to demonstrate the superiority of one or more doses of the Melt formulation of desmopressin to placebo in reducing the mean number of nocturnal voids in a broad population of adult patients with nocturia after 28 days of treatment; (2) to demonstrate the superiority of one or more doses of the Melt formulation of desmopressin to placebo in the proportion of subjects with >33% reduction from baseline in mean number of nocturnal voids after 28 days of treatment; and (3) treatment safety.

[0041] The primary objectives of Part II of this study (extension study) were: (1) to demonstrate the durability of effect achieved in Part I of one or more doses of desmopressin Melt; and (2) treatment safety.

[0042] The secondary objective of both Parts I and II was: to compare the effect of several doses of desmopressin Melt to placebo on sleep disturbance and quality of life.

Overall Study Design

[0043] This was a 2-part (Parts I and II), randomized, double-blind, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of 4 doses of a fast-dissolving ("Melt") formulation of desmopressin for the treatment of nocturia in adults. All treatments were administered orally once per night approximately 1 hour prior to bedtime; subjects were instructed to limit their fluid intake prior to drug self-administration. In Part I, subjects were randomly assigned to 1 of 5 treatment groups: placebo or desmopressin Melt 10 µg, 25 µg, 50 µg, or 100 µg. Randomization was to be stratified by age (<65, ≥65 years) and by the absence/presence of nocturnal polyuria, defined as a ratio of nighttime urine volume/24-hour urine volume ≥33%. To achieve the desired number of subjects within each stratum, enrollment of subjects in a particular stratum (age and/or presence/absence of nocturnal polyuria) could be halted. If this was necessary, all investigative sites were to be informed in writing at least 1 week in advance to stop screening in a population of subjects.

[0044] A total of 750 subjects were planned to be enrolled, with approximately 150 subjects per treatment group. Part I of the study was conducted in 7 visits. Screening (Visit 1) occurred within 21 days of dosing (Day 1, Visit 2); subjects returned for follow-up visits on Days 4, 8, 15, 22, and 28 (end of Part I). Duration of treatment in Part I was 28 days.

[0045] Immediately upon completion of Part I of the study, all subjects on active treatment continued into Part II on the same treatment for approximately 1 to 6 months. Subjects assigned to placebo in Part I were randomly assigned to 1 of the 4 active treatments in Part II. To ensure that the study remained fully blinded during the full extent of both Parts I and II, re-randomization of subjects assigned to placebo after 4 weeks of treatment was predetermined at the time of initial randomization.

[0046] Subjects began Part II at the Final Visit for Part I (Day 28) and returned for follow-up visits on Days 4, 8, 15, 29, and every 4 weeks thereafter until the database was locked for Part I and the treatment groups were unblinded. The total treatment duration for each subject depended on when that subject was randomized in Part I and was estimated to be a minimum of 4 weeks and a maximum of 6 months.

[0047] Upon completion of Part II of the study, subjects were given the option to participate in an open-label study with expected total treatment duration (double-blind extension plus open-label study) of at least 12 months (i.e., Part III). In Part III, subjects were assigned to the same treatment as in Part II, initially in a blinded manner. Subjects were unblinded and the study became open label only when all subjects in Parts I and II remaining in the study had entered Part III. During Part III, 10 µg was identified as a sub-therapeutic dose based on efficacy data from Part I. As a consequence, patients in the 10 µg treatment group were re-randomized (beginning Q4 2008) to one of the other treatment groups (i.e., 25 µg, 50 µg, or 100 µg). The total treatment duration was at least 12 months.

[0048] A total of 508 patients entered the open-labeled extension (i.e., Part III). In total, 367 patients had ≥ 1 year of treatment.

Selection of Doses in Study

[0049] A previous clinical program investigating the efficacy and safety of a Tablet formulation of desmopressin for nocturia utilized doses of 100 µg, 200 µg, and 400 µg. All 3 doses demonstrated a clear effect on pharmacodynamic and clinical endpoints. Although the use of a dose-titration scheme limits the interpretation of dose response, doses higher than 100 µg offered only a marginal improvement in efficacy.

[0050] The dose relationship between the Tablet and Melt formulations was investigated in an open-label, randomized crossover study in which 28 healthy subjects were administered 240 µg Melt and 400 µg Tablet (given as 2x200 µg Tablets) separated by 7 days. AUC, C_{max}, T_{max} and t_{1/2} were similar, indicating that 100 µg Tablet provides an exposure similar to that of 60 µg Melt.

[0051] The present study investigated dose levels substantially lower than those used in the Tablet study. While there are no data with the Melt formulation in the target population to guide dose selection for doses below 100 µg tablet/60 µg Melt, pharmacokinetic (PK) and pharmacodynamic (PD) studies have been conducted in water-loaded healthy subjects and water-loaded children 6 to 12 years of age with nocturnal enuresis. Based on data from these 2 studies, a model simulating PK and PD has been developed. If antidiuretic activity is defined in terms of duration of urine osmolality greater than 200 mOsm/kg, the model indicates that a dose of 10 µg Melt may potentially be subtherapeutic and doses of 25 µg to 100 µg should provide 2.75 to 8.5 hours of antidiuretic activity.

Selection of Study Population: Inclusion Criteria

[0052] Subjects who met the following inclusion criteria were eligible for the study: provided written informed consent prior to the performance of any study-related activity, defined as any procedure that would not have been performed during the normal management of the subject; and was a male or female subject, 18 years of age and older, with an average of ≥2 nocturnal voids per night determined via a 3-day frequency-volume chart during the screening period

Exclusion Criteria

[0053] The presence of any of the following excluded a subject from study enrollment:

Genitourinary Tract Conditions

Males:

[0054] Clinical suspicion of bladder outlet obstruction and/or urine flow <5 mL/sec. If medical history and/or physical examination suggested bladder outlet obstruction, uroflowmetry was to be performed to confirm the diagnosis.

[0055] Surgical treatment, including transurethral ablative treatments, for bladder outlet obstruction/benign prostatic hyperplasia (BPH) performed within the past 6 months.

Females:

[0056] Pregnancy; females of reproductive age were to document they were using a reliable method of contraception.

[0057] Use of pessary for pelvic prolapse.

[0058] Presence of unexplained pelvic mass.

Males and Females:

[0059] Clinical suspicion of urinary retention and/or post-void residual volume >150 mL; if medical history and/or physical examination suggested urinary retention, bladder ultrasound or catheterization was to be performed to confirm the diagnosis.

[0060] Current or past urologic malignancies (e.g., bladder cancer, prostate cancer).

[0061] Clinical evidence of current genitourinary tract pathology that could interfere with voiding.

[0062] History of neurogenic detrusor activity (previously known as detrusor hyperreflexia).

Systemic Medical Conditions

[0063] Suspicion or evidence of cardiac failure.

[0064] Uncontrolled hypertension.

[0065] Uncontrolled diabetes mellitus.

[0066] Renal insufficiency; serum creatinine was to be within normal limits and estimated glomerular filtration rate (eGFR) was to be ≥ 60 mL/min.

[0067] Hepatic and/or biliary disease; aspartate transaminase (AST) and/or alanine transaminase (ALT) were not to be $> 2 \times$ upper limit of normal (ULN) and total bilirubin was not to be > 1.5 mg/dL.

[0068] Hyponatraemia; serum sodium level was to be within normal limits as defined by the Sponsor and central laboratory.

[0069] Diabetes insipidus (urine output > 40 mL/kg over 24 hours).

[0070] Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

[0071] Psychogenic or habitual polydipsia.

[0072] Obstructive sleep apnea requiring therapy.

Other

[0073] Known alcohol or substance abuse.

[0074] Work or lifestyle that potentially interfered with regular nighttime sleep (e.g., shift workers).

[0075] Previous desmopressin treatment for nocturia.

[0076] Any other medical condition, laboratory abnormality, psychiatric condition, mental incapacity, or language barrier that, in the judgment of the Investigator, rendered the subject unsuitable for a clinical trial or impaired subject participation in the study.

[0077] Use of loop diuretics (furosemide, torsemide, ethacrynic acid). Other classes of diuretics (thiazides, triamterene, chlorthalidone, amiloride, indapamide) were permitted, either as monotherapy or combination therapy. Subjects using a diuretic were to be encouraged to take it in the morning, if medically feasible.

[0078] Use of any other investigational drug within 30 days of screening.

Discontinuation Criteria

[0079] Any subject with a serum sodium value of 125 mmol/L or less at any point during the study was to be withdrawn

immediately and further evaluated and treated as necessary.

[0080] Subjects had the right to withdraw from the study at any time for any reason without providing justification. However, the Investigator was to take appropriate steps to ensure that withdrawal was accomplished in a safe manner. A subject could also be discontinued at the discretion of the Investigator or Sponsor because of safety concerns or if judged noncompliant with the study procedures to an extent that could affect the study results. The Investigator and the Sponsor were to agree on subject discontinuation prior to withdrawal, and unnecessary withdrawal of subjects was to be avoided.

[0081] Subjects discontinued from the study were to be scheduled for an End-of-Study (EoS) assessment as soon as possible after the decision to withdraw the subject had been made. For any discontinuation, the Investigator was to obtain all the required data and document the date of the premature withdrawal and the main reason in the electronic case report form (eCRF). If the reason for withdrawal was an adverse event (AE), the specific event or laboratory abnormality was to be recorded in the eCRF. The Investigator was to make a thorough effort to document the outcome. Discontinued subjects were not replaced.

Treatments Administered

[0082] Study drug was administered as an orally disintegrating tablet of desmopressin (desmopressin Melt) or placebo.

[0083] Subjects were randomly assigned to 1 of 5 fixed-dose treatment groups in Part I: placebo or desmopressin Melt 10 µg, 25 µg, 50 µg, or 100 µg. All treatments were administered orally once per night approximately 1 hour prior to bedtime. Subjects were instructed to place the tablet under their tongue, without water. Subjects were provided with sufficient study drug for the duration of Part I.

Study Endpoints

[0084] The primary endpoints for efficacy assessment were: (1) change in mean number of nocturnal voids from baseline evaluation to final visit (Day 28); and (2) proportion of subjects with >33% reduction in the mean number of nocturnal voids from baseline to final visit (Day 28). A further description and corresponding data directed to the second primary endpoint (i.e., portion of subjects with >33% reduction in the mean number of nocturnal voids) are not provided herein.

[0085] The secondary efficacy endpoints were: (1) durability of effect achieved in Part I; (2) change in initial period of undisturbed sleep, defined as the elapsed time in minutes from going to bed with the intention of sleeping to the time of awakening for the first nocturnal void; and (3) change in duration of total sleep time. Additional secondary endpoints were collected, e.g., change in nocturia-specific quality of life as assessed by scores on the International Consultation on Incontinence Modular Questionnaire-Nocturia and the Nocturia Quality of Life Questionnaire, change in quality of sleep as assessed by the global score of the Pittsburg Sleep Quality Index, and change in overall quality of life as assessed by the short form-12v2. A description of the additional secondary efficacy endpoints and their accompanying data are not provided herein.

[0086] Changes in urine volume from baseline to the end of Day 28 were also assessed and included herein.

Flow Chart

[0087] A study flow chart, showing study assessments and procedures conducted at each study visit, are presented in Table 1 for Part I.

Table 1 - Study flow chart for Part I.

Visit	(screening) 1	(randomization) 2	3	4	5	6	7 (EoS) ^a
Week	≤21 days of Visit			1	2	3	4
Procedure	2	1	4	8	15±3	22±3	28±3
Informed consent	X ^b						
Inclusion/exclusion criteria	X						

Visit	(screening) 1	(randomization) 2	3	4	5	6	7 (EoS) ^a
Week	≤21 days of Visit			1	2	3	4
Procedure	2	1	4	8	15±3	22±3	28±3
Login to WebEZ for Subject ID number	X						
Demographic/medical history	X						
Body weight	X						X
Height	X						
Physical examination	X						X
Vital signs (BP, pulse)	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Labs: chemistry (including serum sodium), hematology, urinalysis	X						X
Urine osmolality ^c (exploratory)	X						
Urine pregnancy test	X						X
Uroflowmetry (males only) ^d	X						
Assess post void residual volume ^d	X						
Dispense sleep/voiding diary (3 days) ^e	X						X
Actigraphy ^f	X						X
Adverse events		X	X	X	X	X	X
Review voiding and/or sleep diary		X		X	X	X	X
Nocturia questionnaires: ICIQ-N, PSQI, NQoL, SF-12v2		X					X
Randomization via WebEZ		X					
Dispense voiding diary (3 days) ^e			X	X	X		
Serum sodium			X	X	X	X	
Study drug accountability			X	X	X	X	X
Dispense study drug for Part II (kit number assigned via WebEZ)							X

EoS = End of Study; WebEZ = web-based centralized patient randomization system; BP = blood pressure; ICIQ-N = International Consultation on Incontinence questionnaire-Nocturia; PSQI = Pittsburgh Sleep Quality Index; NQoL = Nocturia Quality of Life; SF-12v2 = Short Form-12, version 2

a. Discontinued subjects were to complete an End-of-Study Visit as soon as possible after study discontinuation.

b. Written informed consent was to be obtained prior to any study-related procedures.

c. Collection of first night-time urine void prior to randomization visit.

d. Uroflowmetry was collected in males only if there was suspicion of obstruction; post residual urine volume was measured using an ultrasound only if there was clinical suspicion of urinary retention.

e. Voiding diaries were completed for 3 consecutive 24-hour cycles; diaries for Weeks 1, 2, and 3 only required the "wake time" of the night-time void.

f. Actigraphy was used in a subset of subjects (at 6 study sites).

Disposition of Subjects

[0088] A total of 1412 subjects were screened for Part I of the study; 613 subjects were screening failures and 799 subjects were randomized to treatment. The most common recorded reasons for screening failure were renal insufficiency (15%) and not averaging ≥ 2 nocturnal voids over the 3-day screening period (10%). A total of 710 (89%) subjects completed Part I of the study and 89 (11%) subjects prematurely discontinued. Across treatment groups, 6% to 16% of subjects prematurely discontinued. The most common reasons for discontinuation overall were withdrawal of consent (4%), adverse event (2%), and lost to follow-up (2%).

Data Sets Analyzed

[0089] Of the 799 randomized subjects in Part I, 757 subjects who received at least 1 dose of study drug and had follow-up data were included in the intent to treat (ITT) analysis dataset. Overall, 10% of ITT subjects had a major protocol violation and were excluded from the per-protocol (PP) analysis dataset. Of the 682 PP subjects, 10% did not have both screening and final visit data on number of nocturnal voids and were excluded from the observed cases (OC) analysis dataset. All 799 randomized subjects received at least 1 dose of study drug (desmopressin or placebo) and had at least 1 safety assessment and, therefore, were included in the safety analysis dataset.

PRIMARY EFFICACY ENDPOINT

Number of Nocturnal Voids

[0090] The mean number of nocturnal voids decreased from baseline to Day 28 in all treatment groups, with greater decreases observed with increasing dose of desmopressin. The reduction in mean number of nocturnal voids, compared to placebo, was statistically significant for the 100 μ g ($p<0.0001$) and 50 μ g ($p=0.0207$) groups.

[0091] The trend of greater decreases in mean number of nocturnal voids with increasing dose of desmopressin was evident in subjects stratified by age (<65 years, ≥ 65 years) and in subjects with nocturnal polyuria. Too few subjects (13 to 18 subjects per treatment group) did not have nocturnal polyuria to make meaningful comparisons. The reduction in mean number of nocturnal voids, compared to placebo, was statistically significant for the 100 μ g group for all 4 stratification factors and for the 50 μ g group for subjects with nocturnal polyuria.

[0092] A summary of changes from baseline to the final visit in the number of nocturnal voids is presented for all groups (ITT population) in Table 2.

Table 2 - Change from baseline to final visit (Day 28) of nocturnal voids (ITT analysis dataset in Part I) for all groups.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	156	-0.86	1.05	0.08	-4.00	-0.83	1.67
10 ug	155	-0.83	1.07	0.09	-4.33	-0.67	2.33
25 ug	152	-1.00	1.13	0.09	-3.67	-1.00	2.33
50 ug	148	-1.18	1.19	0.10	-5.00	-1.00	2.00
100 ug	146	-1.43	1.22	0.10	-5.00	-1.33	4.33
Total	757	-1.05	1.15	0.04	-5.00	-1.00	4.33

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0093] Mean decreases in the number of nocturnal voids were observed by Day 8, with a trend for greater decreases with increasing desmopressin doses; these findings continued at Day 15 and Day 22. Notably, compared to placebo, statistically significant differences were observed for the 25 μ g, 50 μ g, and 100 μ g doses on Day 8 and Day 15 of treatment, with significant differences for the 2 higher doses also on Day 22 and Day 28. Weekly change from baseline in mean number of nocturnal voids, along with p-values for each desmopressin Melt dose compared to placebo, is displayed in Figure 1.

[0094] Among females, the reduction in mean number of nocturnal voids, compared to placebo, was statistically significant for the 100 µg (p<0.0001), 50 µg (p=0.0091), and 25 µg (p=0.0200) groups. Thus, among females, efficacy was demonstrated for the primary endpoint of nocturnal voids for all but the lowest dose of desmopressin.

[0095] A summary of changes from baseline to the final visit in the number of nocturnal voids is presented for all females, females over 50 years of age, and females over 65 years of age (ITT population) in Tables 3, 4 and 5.

Table 3 - Change from baseline to final visit (Day 28) of nocturnal voids (ITT analysis dataset in Part I) for all females.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	66	-0.88	1.01	0.12	-3.33	-0.67	1.00
10 ug	73	-1.15	1.07	0.13	-4.33	-1.00	1.00
25 ug	65	-1.22	1.06	0.13	-3.33	-1.33	1.00
50 ug	71	-1.23	1.06	0.13	-4.00	-1.00	2.00
100 ug	66	-1.51	1.14	0.14	-5.00	-1.33	1.00
Total	341	-1.20	1.08	0.06	-5.00	-1.00	2.00

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0096] Although not statistically significant for the 10 µg group but statistically significant for the 25 µg group, there was a decrease observed in the median number of nocturnal voids identified in Table 3 for all females. For example, the 10 µg and 25 µg groups exhibited at least 1.0 fewer nocturnal urinary voids per night on desmopressin treatment compared to baseline before treatment. The placebo exhibited only 0.67 fewer nocturnal urinary voids per night compared to baseline.

Table 4 - Change from baseline to final visit (Day 28) of nocturnal voids (ITT analysis dataset in Part I) for females over 50 years of age.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	45	-0.74	0.93	0.14	-2.67	-0.67	1.00
10 ug	51	-1.08	1.04	0.15	-4.33	-1.00	0.33
25 ug	49	-1.35	1.04	0.15	-3.33	-1.33	1.00
50 ug	55	-1.15	1.13	0.15	-4.00	-1.00	2.00
100 ug	48	-1.44	1.24	0.18	-5.00	-1.33	1.00
Total	248	-1.16	1.10	0.07	-5.00	-1.00	2.00

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0097] Although not statistically significant for the 10 µg group but statistically significant for the 25 µg group, there was a decrease observed in the median number of nocturnal voids identified in Table 4 for females over 50 years of age. For example, the 10 µg and 25 µg groups exhibited at least 1.0 fewer nocturnal urinary voids per night on desmopressin treatment compared to baseline before treatment. The placebo exhibited only 0.67 fewer nocturnal urinary voids per night compared to baseline.

Table 5 - Change from baseline to final visit (Day 28) of nocturnal voids (ITT analysis dataset in Part I) for females over 65 years of age.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	21	-0.51	0.73	0.16	-2.33	-0.33	0.67
10 ug	25	-0.93	1.07	0.21	-4.33	-0.67	0.33
25 ug	22	-1.27	0.99	0.21	-2.67	-1.67	1.00
50 ug	20	-0.97	0.95	0.21	-2.33	-1.00	1.33
100 ug	25	-1.00	1.18	0.24	-3.00	-1.00	1.00
Total	113	-0.94	1.02	0.10	-4.33	-1.00	1.33

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0098] Similarly to the other female groups, there was a decrease observed in the median number of nocturnal voids identified in

Table 5 for females over 65 years of age at the 25 µg group. For example, the 25 µg group exhibited at least 1.67 fewer nocturnal urinary voids per night on desmopressin treatment compared to baseline before treatment. The placebo exhibited only 0.33 fewer nocturnal urinary voids per night compared to baseline.

[0099] Among males, statistically significant differences from placebo were observed for the 100 µg group in the reduction in mean number of nocturnal voids ($p=0.0049$).

[0100] A summary of the changes from baseline to the final visit in the number of nocturnal voids is presented for all males and all males with monitoring (ITT population) in Tables 6 and 7.

Table 6 - Change from baseline to final visit (Day 28) of nocturnal voids (ITT analysis dataset in Part I) for all males.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	90	-0.84	1.09	0.12	-4.00	-1.00	1.67
10 ug	82	-0.54	0.99	0.11	-3.00	-0.67	2.33
25 ug	87	-0.83	1.15	0.12	-3.67	-0.67	2.33
50 ug	77	-1.13	1.30	0.15	-5.00	-1.00	1.33
100 ug	80	-1.38	1.28	0.14	-4.33	-1.33	4.33
Total	416	-0.94	1.19	0.06	-5.00	-1.00	4.33

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

Table 7 - Change from baseline to final visit (Day 28) of nocturnal voids (ITT analysis dataset in Part I) for all males with monitoring.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	74	-0.88	1.15	0.13	-4.00	-1.00	1.67
10 ug	66	-0.66	0.97	0.12	-3.00	-0.67	1.33
25 ug	72	-0.91	1.16	0.14	-3.67	-0.67	2.33
50 ug	52	-1.09	1.26	0.17	-5.00	-1.00	1.33
100 ug	60	-1.41	1.35	0.17	-4.33	-1.67	4.33
Total	324	-0.97	1.19	0.07	-5.00	-1.00	4.33

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0101] The differences among males and females in the change in number of nocturnal voids is illustrated in Figure 2. In Figure 2, the mean observed (full line) and predicted (broken line) change in number of voids by gender and dose demonstrate that the 10 µg and 25 µg groups for females exhibit a larger decrease in nocturnal voids compared to the 10 µg and 25 µg groups for males. The side-by-side comparison in Figure 2 highlights the gender and dose differences without the requirement of statistical significance.

[0102] Based on these gender differences, the minimum effective dose (MED) for females is 25 µg and the MED for males is 100 µg.

Long Term Data - Nocturnal Voids

[0103] At one year (Part III), the mean decrease in nocturnal voids per night was 1.4, 1.77, and 2.11 (for 25 µg, 50 µg, and 100 µg, respectively) based on all eligible subjects. The mean decreases in nocturnal voids demonstrate that the decrease observed for the respective concentrations at Day 28 (i.e., Part I) are maintained over a longer treatment period (e.g., 52 weeks) and in some instances, are even improved. A summary of the changes from baseline is presented for all eligible subjects. With respect to this particular data for Part III, "all eligible subjects" means those subjects that continued through Parts I, II, and III of the study on the same dose (i.e., re-randomized placebo subjects have been excluded) and completed the 1 year diary.

[0104] Applicants note that statistical significance cannot be demonstrated for the Part III data on nocturnal voids, as the placebo group was not maintained for Part III. However, based on the data below, the additional decreases in the number of voids can be characterized as clinically significant. As used here, "clinically significant" means a minimum worthwhile effect.

[0105] A summary of changes from baseline to day 28 and to week 52 in the number of nocturnal voids is present for all eligible groups in Tables A, B, and C for the 25 µg, 50 µg, and 100 µg doses of desmopressin.

Table A - Baseline at day 0 and changes from baseline nocturnal voids for all eligible subjects at the 25 µg dosage.

	n	Mean	Std Dev	Min	Max
Day 0	86	3.24	1.27	2.00	8.67
Day 28	86	-0.98	1.15	-3.33	2.33
Week 8	67	-1.16	1.13	-3.33	2.67
Week 12	57	-1.29	1.14	-3.00	1.33
Week 20	42	-1.48	1.05	-3.67	1.67
Week 28	67	-1.44	1.20	-4.33	1.00
Week 52	86	-1.41	1.26	-4.67	2.33

n - population size; stddev - standard deviation; min - minimum; and max - maximum

Table B - Baseline at day 0 and changes from baseline for all eligible subjects at the 50 µg dosage.

	n	Mean	Std Dev	Min	Max
Day 0	76	3.42	1.08	2.00	7.00
Day 28	76	-1.22	1.20	-5.00	2.00
Week 8	58	-1.44	1.05	-4.00	1.33
Week 12	51	-1.44	1.09	-3.67	1.00
Week 20	48	-1.80	1.12	-4.00	1.00
Week 28	44	-1.55	1.21	-5.00	1.00
Week 52	76	-1.80	1.31	-6.67	0.33

n - population size; stddev - standard deviation; min - minimum; and max - maximum

Table C - Baseline at day 0 and changes from baseline for all eligible subjects at the 100 µg dosage.

	n	Mean	Std Dev	Min	Max
Day 0	73	3.30	1.11	2.00	7.00
Day 28	73	-1.406	1.26	-5.00	4.33
Week 8	62	-1.61	1.11	-5.00	0.67
Week 12	46	-1.83	1.12	-5.00	0.33
Week 20	43	-1.95	1.12	-5.33	0
Week 28	47	-1.83	0.86	-4.67	-0.33
Week 52	73	-2.11	1.14	-6.33	0.67

n - population size; stddev - standard deviation; min - minimum; and max-maximum

[0106] Although not statistically significant, the change from baseline to Week 52 in comparison to the change of baseline to day 28 demonstrates that for all eligible subjects, the decrease in frequency of nocturnal voids can be maintained and/or improved over a longer treatment period in a clinically significant manner.

[0107] Among females, the reduction in mean number of nocturnal voids from baseline to week 52 maintained or improved, particularly at the 25 µg dose. A summary of changes from baseline to week 52 in the number of nocturnal voids is presented for all females in Tables D-F for the 25 µg, 50 µg, and 100 µg doses of desmopressin.

Table D - Baseline at day 0 and changes from baseline for all eligible female subjects at the 25 µg dosage.

	n	Mean	Std Dev	Min	Max
Day 0	38	3.23	1.31	2.00	8.67
Day 28	38	-1.26	1.06	-3.33	0.67
Week 8	32	-1.51	0.83	-3.00	0

	n	Mean	Std Dev	Min	Max
Week 12	29	-1.66	0.98	-3.00	0.67
Week 20	22	-1.68	0.96	-3.00	0.67
Week 28	27	-1.86	1.18	-4.33	0.33
Week 52	38	-1.75	1.16	-4.67	2.00

n - population size; stddev - standard deviation; min - minimum; and max - maximum

Table E - Baseline at day 0 and changes from baseline of nocturnal voids for all eligible female subjects at the 50 µg dosage.

	n	Mean	Std Dev	Min	Max
Day 0	31	3.17	0.70	2.00	4.67
Day 28	31	-1.30	1.16	-4.00	2.00
Week 8	26	-1.60	1.045	-4.00	1.00
Week 12	23	-1.62	1.072	-3.33	0.67
Week 20	18	-1.93	1.11	-3.67	0.33
Week 28	19	-1.89	0.88	-3.33	0
Week 52	31	-1.95	0.77	-3.67	-0.33

n - population size; stddev - standard deviation; min - minimum; and max-maximum

Table F - Baseline at day 0 and changes from baseline of nocturnal voids for all eligible female subjects at the 100 µg dosage.

	n	Mean	Std Dev	Min	Max
Day 0	37	3.08	1.12	2.00	7.00
Day 28	37	-1.50	1.22	-5.00	1.00
Week 8	32	-1.69	1.27	-5.00	0.33
Week 12	27	-1.79	1.23	-5.00	0.33
Week 20	22	-1.98	1.29	-5.33	0
Week 28	26	-1.75	1.01	-4.67	-0.33
Week 52	37	-2.11	1.35	-6.33	0.67

n - population size; stddev - standard deviation; min - minimum; and max-maximum

[0108] Among males, decreases in mean nocturnal voids from baseline to week 52 were observed. A summary of the changes from baseline to week 52 is presented for all eligible male subjects in Tables G-I.

Table G - Baseline at day 0 and changes from baseline of nocturnal voids for all eligible male subjects at the 25 µg dosage.

	n	Mean	Std Dev	Min	Max
Day 0	48	3.26	1.24	2.00	6.33
Day 28	48	-0.76	1.18	-2.67	2.33
Week 8	35	-0.84	1.27	-3.33	2.67
Week 12	28	-0.90	1.19	-2.67	1.33
Week 20	20	-1.25	1.13	-3.67	1.67
Week 28	40	-1.15	1.13	-3.67	1.00
Week 52	48	-1.13	1.28	-4.33	2.33

n - population size; stddev - standard deviation; min - minimum; and max-maximum

Table H - Baseline at day 0 and changes from baseline of nocturnal voids for all eligible male subjects at the 50 µg dosage.

	n	Mean	Std Dev	Min	Max
Day 0	45	3.59	1.25	2.00	7.00
Day 28	45	-1.16	1.23	-5.00	1.00
Week 8	32	-1.31	1.04	-3.67	1.33

	n	Mean	Std Dev	Min	Max
Week 12	28	-1.30	1.11	-3.67	1.00
Week 20	30	-1.73	1.13	-4.00	1.00
Week 28	25	-1.28	1.37	-5.00	1.00
Week 52	45	-1.69	1.58	-6.67	0.33

n - population size; stddev - standard deviation; min - minimum; and max-maximum

Table I - Baseline at day 0 and changes from baseline of nocturnal voids for all eligible male subjects at the 100 µg dosage.

	n	Mean	Std Dev	Min	Max
Day 0	36	3.53	1.07	2.00	6.00
Day 28	36	-1.31	1.31	-3.67	4.33
Week 8	30	-1.52	0.90	-3.00	0.67
Week 12	19	-1.89	0.96	-3.33	0.33
Week 20	21	-1.92	0.93	-3.33	-0.33
Week 28	21	-1.92	0.64	-3.500	-1.00
Week 52	36	-2.12	0.89	-4.00	-0.33

n - population size; stddev - standard deviation; min - minimum; and max-maximum

[0109] Tables J-L summarize the data for all subjects with or without an assessment at week 52.

Table J - Baseline at day 0 and changes from baseline of nocturnal voids for all subjects at the 25 µg dosage.

	n	Mean	Std Dev	Minimum	Maximum
Day 0	158	3.38	1.35	2.00	8.67
Day 28	158	-0.96	1.12	-3.67	2.33
Week	100	-1.31	1.16	-4.67	2.67
Week 12	85	-1.42	1.23	-5.00	2.00
Week 20	60	-1.61	1.16	-6.00	1.67
Week 28	87	-1.39	1.14	-4.33	1.33
Week 52	86	-1.41	1.26	-4.67	2.33

n - population size; stddev - standard deviation; min - minimum; and max-maximum

Table K - Baseline at day 0 and changes from baseline of nocturnal voids for all subjects at the 50 µg dosage.

	n	Mean	Std Dev	Minimum	Maximum
Day 0	157	3.39	1.05	2.00	7.33
Day	157	-1.10	1.19	-5.00	2.00
Week	92	-1.43	1.28	-6.33	2.33
Week 12	77	-1.51	1.16	-4.00	1.33
Week 20	64	-1.71	1.16	-4.00	1.00
Week 28	61	-1.55	1.28	-5.00	1.67
Week 52	76	-1.80	1.31	-6.67	0.33

n - population size; stddev - standard deviation; min - minimum; and max-maximum

Table L - Baseline at day 0 and changes from baseline of nocturnal voids for all subjects at the 100 µg dosage.

	n	Mean	Std Dev	Minimum	Maximum
Day 0	160	3.22	1.06	2.00	7.33
Day 28	160	-1.31	1.23	-5.00	4.33
Week 8	104	-1.47	1.08	-5.00	0.67

	n	Mean	Std Dev	Minimum	Maximum
Week 12	81	-1.73	1.04	-5.00	0.33
Week 20	64	-1.86	1.08	-5.33	0
Week	61	-1.80	0.90	-4.67	0.67
Week 52	73	-2.11	1.14	-6.33	0.67

n - population size; stddev - standard deviation; min - minimum; and max - maximum

SECONDARY EFFICACY ENDPOINTS

[0110] The secondary efficacy variables were changes from baseline in duration of initial period of undisturbed sleep, duration of total sleep time, and changes in nocturnal urine volume. As noted, the additional secondary efficacy variables data collected (i.e., global (overall) scores of the NQoL, PSQL, and SF-12v2, and scores of the ICIQ-N) are not presented herein.

Duration of Initial Period of Undisturbed Sleep

[0111] The most pernicious effect of nocturia is not excessive voiding per se, but its impact on sleep quality and subsequent daytime function as a consequence of sleep disruption. The duration of the initial period of undisturbed sleep increased from baseline to Day 28 in all treatment groups, with greater increases observed with increasing dose of desmopressin. Mean increases in initial sleep duration were 83, 85, and 107 minutes in the 25 µg, 50 µg, and 100 µg groups, respectively. Subjects treated with 25 µg and 50 µg desmopressin had a median increase in their initial period of sleep of approximately 1 hour while subjects treated with the 100 µg dose had a median increase in initial sleep duration of approximately 1½ hours. The 95% confidence intervals for the mean difference from placebo in change from baseline did not include zero for the 25 µg, 50 µg, and 100 µg groups, indicating statistically significant treatment group differences.

[0112] A summary of changes from baseline to the final visit in initial period of undisturbed sleep is presented for all groups (ITT population) in Table 8.

Table 8 - Change from baseline to final visit (Day 28) in duration of initial period of undisturbed sleep (ITT analysis dataset in Part I) for all groups.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	126	39	89	8	-273	42	386
10 ug	126	51	111	10	-317	51	457
25 ug	121	83	106	10	-104	62	413
50 ug	123	85	109	10	-233	63	453
100 ug	121	107	116	11	-166	96	399
Total	617	72	109	4	-317	60	457

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0113] Although not statistically significant, an increase in the initial period of undisturbed sleep is evident for the 10 µg group as compared to placebo based on median values identified in Table 8 for all groups. For example, the 10 µg group exhibited a median increase of 51 minutes compared to baseline before treatment. The placebo exhibited only a median increase of 42 minutes compared to baseline. Taking into consideration a 5% range from the median increase for the 10 µg group, increases in an initial period of undisturbed sleep range from 48 minutes to 54 minutes compared to baseline before treatment.

[0114] A summary of changes from baseline to the final visit in initial period of undisturbed sleep is presented for all females, females over 50 years of age, and females over 65 years of age (ITT population) in Tables 9, 10 and 11.

Table 9 - Change from baseline to final visit (Day 28) in duration of initial period of undisturbed sleep (ITT analysis dataset in Part I) for all females.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	49	37	94	13	-168	12	386
10 ug	60	54	117	15	-317	46	457
25 ug	51	113	118	17	-70	95	413
50 ug	61	98	125	16	-233	70	453
100 ug	57	114	130	17	-166	93	399
Total	278	84	121	7	-317	63	457

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0115] Although not statistically significant, an increase in the initial period of undisturbed sleep is evident for the 10 µg and 25 µg groups as compared to placebo based on median values identified in Table 9 for all female patients. For example, the 10 µg group exhibited a median increase of 46 minutes and the 25 µg group exhibited a median increase of 95 minutes compared to baseline before treatment. The placebo exhibited only a median increase of 12 minutes compared to baseline. Taking into consideration a 20% range from the median increase for the 10 µg and 25 µg groups, increases in an initial period of undisturbed sleep ranges from 37 minutes to 114 minutes, such as from 37 minutes to 55 minutes for the 10 µg group and from 76 minutes to 114 minutes for the 25 µg group compared to baseline for all females.

Table 10 - Change from baseline to final visit (Day 28) in duration of initial period of undisturbed sleep (ITT analysis dataset in Part I) for females over 50 years of age.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	38	25	77	13	-168	11	168
10 ug	40	33	112	18	-317	27	293
25 ug	39	122	123	20	-70	96	413
50 ug	48	83	126	18	-233	63	453
100 ug	42	108	129	20	-166	89	330
Total	207	75	121	8	-317	54	453

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0116] Although not statistically significant, an increase in the initial period of undisturbed sleep is evident for the 10 µg and 25 µg groups as compared to placebo based on median values identified in Table 10 for female patients over 50 years of age. For example, the 10 µg group exhibited a median increase of 27 minutes and the 25 µg group exhibited a median increase of 96 minutes compared to baseline before treatment. The placebo exhibited only a median increase of 11 minutes compared to baseline. Taking into consideration a 20% range from the median increase for the 10 µg and 25 µg groups, increases in an initial period of undisturbed sleep ranges from 22 minutes to 115 minutes, such as from 22 minutes to 32 minutes for the 10 µg group and from 77 minutes to 115 minutes for the 25 µg group, compared to baseline before treatment for females over 50 years of age.

Table 11 - Change from baseline to final visit (Day 28) in duration of initial period of undisturbed sleep (ITT analysis dataset in Part I) for females over 65 years of age.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	19	50	60	14	-50	52	168
10 ug	18	18	125	29	-317	46	243
25 ug	15	131	126	32	-70	113	413
50 ug	19	42	131	30	-233	30	288
100 ug	21	81	119	26	-118	70	275
Total	92	62	118	12	-317	53	413

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0117] Although not statistically significant, an increase in the initial period of undisturbed sleep is evident for the 25 µg group as

compared to placebo based on median values identified in Table 11 for female patients over 65 years of age. For example, the 25 µg group exhibited a median increase of 113 minutes compared to baseline before treatment. The placebo exhibited only a median increase of 52 minutes compared to baseline. Taking into consideration a 20% range from the median increase for the 25 µg group, increases in an initial period of undisturbed sleep range from 90 minutes to 136 minutes, such as from 102 minutes to 124 minutes, compared to baseline before treatment for females over 65 years of age.

[0118] A summary of changes from baseline to the final visit in initial period of undisturbed sleep is presented for all males and all males with monitoring (ITT population) in Tables 12 and 13.

Table 12 - Change from baseline to final visit (Day 28) in duration of initial period of undisturbed sleep (ITT analysis dataset in Part I) for all males.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	77	40	86	10	-273	47	285
10 ug	66	48	107	13	-158	56	370
25 ug	70	61	90	11	-104	55	259
50 ug	62	72	90	11	-165	55	292
100 ug	64	100	103	13	-152	101	363
Total	339	63	97	5	-273	58	370

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

Table 13 - Change from baseline to final visit (Day 28) in duration of initial period of undisturbed sleep (ITT analysis dataset in Part I) for all males with monitoring.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	70	44	85	10	-273	48	285
10 ug	60	54	107	14	-145	59	370
25 ug	62	57	87	11	-104	54	259
50 ug	45	64	89	13	-165	59	291
100 ug	52	108	103	14	-152	116	363
Total	289	64	96	6	-273	58	370

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

Duration of Total Sleep Time

[0119] Total sleep time increased in all treatment groups in Part I; however, no pattern was observed by dose of desmopressin. Based on F-tests of effects, computed overall sleep duration and reported overall sleep duration were statistically significant predictors of change from baseline to Day 28 in total sleep time ($p<0.0001$).

[0120] A summary of change from baseline to Day 28 in total sleep time is presented by treatment group in Table 14.

Table 14 - Change from baseline to final visit (Day 28) in total sleep time (Part I).

Total Sleep Time (min)	Placebo (N=156)	10 µg (N=155)	25 µg (N=152)	50 µg (N=148)	100 µg (N=146)
Calculated Sleep Time					
Baseline	(N=156)	(N=155)	(N=152)	(N=148)	(N=146)
Mean (SD)	399 (97.0)	397 (92.2)	397 (90.3)	404 (95.8)	414 (85.0)
Median	410	402	412	415	418
Minimum, maximum	(15, 732)	(135, 720)	(95, 577)	(20, 577)	(72, 638)
Change from	(N=138)	(N=137)	(N=142)	(N=138)	(N=133)
Baseline	31.4 (89.22)	9.7 (91.40)	19.7 (71.67)	24.2 (79.60)	9.7 (77.33)
Mean (SD)	19.5	10.0	15.3	14.2	12.0
Median	(-167, 420)	(-332, 282)	(-191, 318)	(-235, 218)	(-300, 227)

Total Sleep Time (min)	Placebo (N=156)	10 µg (N=155)	25 µg (N=152)	50 µg (N=148)	100 µg (N=146)
Minimum, maximum					
Reported Sleep Time					
Baseline	(N=156)	(N=155)	(N=152)	(N=148)	(N=146)
Mean (SD)	403 (83.7)	411 (72.8)	401 (77.8)	403 (83.7)	413 (81.3)
Median	408	400	410	409	410
Minimum, maximum	(135, 625)	(190, 613)	(77, 555)	(100, 580)	(100, 674)
Change from	(N=139)	(N=137)	(N=141)	(N=138)	(N=133)
Baseline	24.6 (80.66)	7.8 (58.55)	15.9 (53.92)	24.9 (72.21)	19.0
Mean (SD)	20.3	10.0	10.0	20.0	(68.94)
Median	(-135, 525)	(-130, 163)	(-113, 228)	(-168, 293)	20.0
Minimum, maximum					(-160, 197)

Change in Urine Volume

[0121] Pharmacodynamic studies indicate that desmopressin has a very pronounced antidiuretic effect. Nocturnal urine volume decreased in all treatment groups, with greater decreases observed with increasing desmopressin dose. For change from baseline to Day 28 in nocturnal urine volume, based on F-tests of effects, treatment ($p<0.0001$), age ($p=0.0067$), and baseline nocturnal urine volume ($p<0.0001$) were statistically significant predictors for change from baseline. The 95% confidence intervals for the mean difference from placebo in change from baseline did not include zero for the 25 µg, 50 µg, and 100 µg groups, indicating statistically significant treatment group differences.

[0122] Similarly, total urine volume, which included both day and nocturnal voids, decreased in all treatment groups, with greater decreases observed with increasing desmopressin dose. In the 50 µg group, a slight mean increase in urine output occurred during the day and, as a result, the nocturnal mean urine reduction was greater than the total mean urine reduction.

[0123] As shown in Figure 3, the majority of the decrease in total urine volume was a decrease in nocturnal volume. The decreases in nocturnal urine volume for the 25 µg, 50 µg, and 100 µg groups were statistically significant.

[0124] A summary of changes from baseline to the final visit in of nocturnal urine volume is presented for all groups (ITT population) in Table 15.

Table 15 - Change from baseline to final visit (Day 28) of nocturnal urine volume (ITT analysis dataset in Part I) for all groups.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	140	-109	246	21	-817	-94	800
10 ug	137	-164	277	24	-983	-150	568
25 ug	144	-224	264	22	-1,084	-233	567
50 ug	138	-272	296	25	-1,017	-233	717
100 ug	135	-312	275	24	-1,238	-283	408
Total	694	-216	281	11	-1,238	-200	800

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0125] Although not statistically significant, a decrease in nocturnal urine volume is evident for the 10 µg group as compared to placebo based on median decreases identified in Table 15 for all groups. For example, the 10 µg group exhibited a median value decrease of 150 ml compared to baseline before treatment. The placebo exhibited only a median decrease of 94 ml compared to baseline. Taking into consideration a 20% range from the median decrease for the 10 µg group, decreases in nocturnal urine volume include at least 120 ml and for example, range from 120 ml to 180 ml, compared to baseline before treatment for all groups.

[0126] A summary of changes from baseline to the final visit of nocturnal urine volume is presented for all females, females over 50 years of age, and females over 65 years of age (ITT population) in Tables 16, 17 and 18.

Table 16 - Change from baseline to final visit (Day 28) of nocturnal urine volume (ITT analysis dataset in Part I) for all females.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	60	-86	278	36	-817	-56	800
10 ug	66	-207	292	36	-983	-179	538
25 ug	61	-307	276	35	-1,084	-298	292
50 ug	66	-257	282	35	-1,017	-204	717
100 ug	60	-321	239	31	-933	-283	25
Total	313	-236	285	16	-1,084	-217	800

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0127] Although not statistically significant, a decrease in nocturnal urine volume is evident for the 10 μ g and 25 μ g groups as compared to placebo based on median decreases identified in Table 16 for all females. For example, the 10 μ g group exhibited a median decrease of 179 ml and the 25 μ g group exhibited a median decrease of 298 ml compared to baseline before treatment. The placebo exhibited only a median decrease of 56 ml compared to baseline. Taking into consideration a 20% range from the median decreases for the 10 μ g and 25 μ g groups, decreases in nocturnal urine volume include at least 143 ml and for example, range from 143 ml to 358 ml, such as from 143 ml to 215 ml for the 10 μ g group and from 238 ml to 358 ml for the 25 μ g group, compared to baseline before treatment for all females.

Table 17 - Change from baseline to final visit (Day 28) of nocturnal urine volume (ITT analysis dataset in Part I) for females over 50 years of age.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	44	-102	242	36	-817	-56	268
10 ug	45	-197	319	48	-983	-150	538
25 ug	46	-356	281	41	-1,084	-383	292
50 ug	52	-249	289	40	-1,017	-196	717
100 ug	45	-317	252	38	-933	-275	25
Total	232	-245	290	19	-1,084	-217	717

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0128] Although not statistically significant, a decrease in nocturnal urine volume is evident for the 10 μ g and 25 μ g groups as compared to placebo based on median decreases identified in Table 17 for females over 50 years of age. For example, the 10 μ g group exhibited a median decrease of 150 ml and the 25 μ g group exhibited a median decrease of 383 ml compared to baseline before treatment. The placebo exhibited a median decrease of 56 ml compared to baseline. Taking into consideration a 20% range from the median decreases for the 10 μ g and 25 μ g groups, decreases in nocturnal urine volume include at least 120 ml and for example, range from 120 ml to 460 ml, such as from 120 ml to 180 ml for the 10 μ g group and from 306 ml to 460 ml for the 25 μ g group, compared to baseline before treatment for females over 50 years of age.

Table 18 - Change from baseline to final visit (Day 28) of nocturnal urine volume (ITT analysis dataset in Part I) for females over 65 years of age.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	20	-90	170	38	-557	-47	133
10 ug	22	-91	302	64	-742	-54	538
25 ug	19	-372	270	62	-867	-383	25
50 ug	20	-208	323	72	-703	-203	717
100 ug	23	-323	261	54	-817	-285	25
Total	104	-216	290	28	-867	-171	717

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0129] Although not statistically significant, a decrease in nocturnal urine volume is evident for the 25 µg group as compared to placebo based on median decreases identified in Table 18 for females over 65 years of age. For example, the 25 µg group exhibited a median decrease of 383 ml compared to the placebo median decrease of 47 ml compared to baseline before treatment. Taking into consideration a 20% range from the median decrease for the 25 µg group, decreases in nocturnal urine volume include at least 211 ml and for example, range from 238 ml to 290 ml, compared to baseline before treatment for females over 65 years of age.

[0130] A summary of changes from baseline to the final visit of nocturnal urine volume is presented for all males and all males with monitoring (ITT population) in Tables 19 and 20.

Table 19 - Change from baseline to final visit (Day 28) of nocturnal urine volume (ITT analysis dataset in Part I) for all males.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	80	-125	219	25	-727	-111	583
10 ug	71	-125	257	30	-750	-117	568
25 ug	83	-162	238	26	-873	-200	567
50 ug	72	-286	309	36	-984	-246	422
100 ug	75	-306	302	35	-1,238	-270	408
Total	381	-199	276	14	-1,238	-192	583

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

Table 20 - Change from baseline to final visit (Day 28) of nocturnal urine volume (ITT analysis dataset in Part I) for all males with monitoring.

Dose	n	mean	stddev	stderr	min	median	max
Placebo	72	-128	229	27	-727	-111	583
10 ug	63	-122	269	34	-750	-83	568
25 ug	72	-146	219	26	-608	-167	567
50 ug	50	-286	313	44	-984	-235	357
100 ug	60	-296	275	36	-867	-264	408
Total	317	-188	268	15	-984	-183	583

n - population size; stddev - standard deviation; stderr - standard error; min - minimum; and max - maximum

[0131] From Table 20, a decrease in nocturnal urine volume is evident for the 100 µg group as compared to placebo based on median decreases from baseline. For example, the 100 µg group exhibited a median decrease of 264 ml compared to baseline before treatment. The placebo exhibited only a median decrease of 111 ml compared to baseline. Taking into consideration a 20% range from the median decrease for the 100 µg group, decreases in nocturnal urine volume include at least 211 ml and for example, range from 211 ml to 317 ml, such as from 238 ml to 290 ml, compared to baseline before treatment for males with monitoring.

[0132] The differences among males and females in the change in nocturnal urine volume is illustrated in Figure 4. In Figure 4, the mean observed (full line) and predicted (broken line) change in nocturnal urine volume demonstrate the greater sensitivity to lower doses (i.e., 10 µg and 25 µg groups) in females than males. The side-by-side comparison in Figure 4 highlights the gender and dose differences without the requirement of statistical significance.

Statistical/Analytical Issues - Handling of Dropouts or Missing Data

[0133] Missing values concerning number of nocturnal voids at Day 8, Day 15, Day 22, and Day 28 in Part I were imputed using last observation carried forward (LOCF). Missing values concerning sleep disturbance and urine volume (for average 24-hour urine volume and average nocturnal urine volume) were not imputed.

Drug Dose, Drug Concentration and Relationships to Response

[0134] Four doses of desmopressin (10 µg, 25 µg, 50 µg, and 100 µg) were included in this study. Both the primary endpoint of the number of nocturnal voids generally demonstrated an increase in efficacy with increasing dose of desmopressin. An additional analysis of the primary efficacy endpoint was performed by gender and demonstrated gender differences in response. Among females, efficacy was demonstrated for the 25 µg, 50 µg, and 100 µg doses of desmopressin for the primary endpoint. Among males, the 100 µg desmopressin dose was superior to placebo for the primary endpoint. Based on these gender differences, the MED for females is 25 µg and for males is 100 µg.

Efficacy Conclusions

[0135] Four doses of desmopressin (10 µg, 25 µg, 50 µg, and 100 µg) were compared to placebo in this study for the primary endpoint in Part I: change in the mean number of nocturnal voids from baseline to final visit (Day 28).

[0136] The mean number of nocturnal voids decreased from baseline to Day 28 in all treatment groups, with greater decreases observed with increasing dose of desmopressin. The reduction in mean number of nocturnal voids, compared to placebo, was statistically significant for the 100 µg and 50 µg groups. The trend of greater decreases in mean number of nocturnal voids with increasing dose of desmopressin was evident in subjects stratified by age (<65 years, ≥65 years) and in subjects with nocturnal polyuria. Too few subjects did not have nocturnal polyuria to make meaningful comparisons. The reduction in mean number of nocturnal voids, compared to placebo, was statistically significant for the 100 µg group for all 4 stratification factors and for the 50 µg group for subjects with nocturnal polyuria. When decreases in mean number of nocturnal voids were examined by week of treatment, statistically significant differences, compared to placebo, were observed for the 25 µg, 50 µg, and 100 µg doses on Day 8 and Day 15 of treatment, with significant differences for the 2 higher doses also on Day 22 and Day 28.

[0137] An additional analysis of the primary efficacy endpoint was performed by gender, and a gender difference in response was observed. Among females, the reduction in mean number of nocturnal voids was statistically significantly superior to placebo for the 100 µg, 50 µg, and 25 µg groups. Among males, statistically significant differences from placebo were observed for the primary endpoint for the 100 µg group. Based on these gender differences, the MED for females is 25 µg and the MED for males is 100 µg.

[0138] Nocturnal urine volume, as well as total urine volume, decreased in all treatment groups, with greater decreases observed with increasing desmopressin dose. Based on 95% confidence intervals that did not include zero, the decreases in nocturnal urine volume for the 25 µg, 50 µg, and 100 µg groups were statistically significant.

[0139] The secondary efficacy endpoint of change from baseline to final visit (Day 28) in duration of initial period of undisturbed sleep also demonstrated greater increases with increasing dose of desmopressin. Subjects treated with 25 µg and 50 µg had a median increase in their initial period of sleep of approximately 1 hour while subjects treated with the 100 µg dose had a median increase in initial sleep duration of approximately 1½ hours; the 95% confidence intervals for the mean difference from placebo indicated statistically significant differences for the 25 µg, 50 µg, and 100 µg groups.

[0140] In summary, the efficacy of 100 µg desmopressin was demonstrated superior to placebo for the primary endpoint overall; for the primary endpoint, among males and among females; proportions of subjects with >50% and >75% reductions in the mean number of nocturnal voids; change from baseline to final visit (Day 28) in duration of the initial period of undisturbed sleep; and reductions in nocturnal urine volume. The efficacy of 50 µg desmopressin was superior to placebo for change from baseline to Day 28 in the mean number of nocturnal voids; for the primary endpoint among females; duration of the initial period of undisturbed sleep; and reductions in nocturnal urine volume. In addition, numerical superiority was observed for 50 µg desmopressin compared to placebo for the proportion of subjects with >33% reductions (53% vs. 47%), >50% reductions (28% vs. 20%), and >75% reductions (10% vs. 5%) in the mean number of nocturnal voids on Day 28. The 25 µg dose was superior to placebo for the primary endpoint among females; in reducing the mean number of nocturnal voids; change from baseline to Day 28 in duration of the initial period of undisturbed sleep; and reductions in nocturnal urine volume. The 10 µg dose did not demonstrate statistically superiority over placebo for the primary or secondary efficacy endpoint. A gender difference in response was observed. For the primary endpoint, superiority to placebo was demonstrated for the 25 µg, 50 µg, and 100 µg doses among females and for the 100 µg dose among males.

[0141] Results of Study CS29 demonstrated that the 100 µg dose was clearly efficacious, while the 10 µg dose can be considered subtherapeutic for the primary efficacy parameter for the overall study population. Based on the observed gender differences, the MED for females is 25 µg and the MED for males is 100 µg.

[0142] At 1 year, the mean decrease in nocturnal voids was 1.4, 1.77, and 2.11 (for 25 µg, 50 µg, and 100 µg, respectively) based on all eligible subjects.

Adverse Events Leading to Discontinuation: Hyponatraemia and Serum Sodium Monitoring

[0143] The reported event of hyponatraemia, defined as serum sodium <130 mmol/L, was an adverse event of special interest. A total of 34 (4%) subjects developed hyponatraemia during Part I. There was essentially no difference in the occurrence of hyponatraemia between placebo and the 10 µg and 25 µg groups; however, the incidence of serum sodium <130 mmol/L rose from 1.3% in the 25 µg group to 7.0% in the 50 µg group and to 11.3% in the 100 µg group. Hyponatraemia tended to occur early in treatment, usually during the first week, and was more common in subjects ≥65 years of age.

[0144] Since hyponatraemia is a potentially serious adverse event associated with daily doses of desmopressin, serum sodium was monitored throughout the study in all subjects. Based on the results of Study CS29, the following sodium monitoring criteria were applied to the CS29 data.

[0145] In subjects below 50 years of age:

Baseline serum sodium level ≥ 135 mmol/L.

[0146] In subjects 50 years of age and above:

Baseline serum sodium level ≥ 135 mmol/L

Day 4 serum sodium level ≥ 135 mmol/L

Day 28 serum sodium level ≥ 135 mmol/L.

[0147] Subjects who did not meet these criteria would be removed. Without monitoring, serum sodium levels below 125 mmol/L occurred in 3 subjects each in the 50 µg and 100 µg groups on Day 4 and 1 subject in each of these groups on Day 8. It should be remembered that serum sodium monitoring occurred the day after the evening dose of study drug.

[0148] Based on these findings, serum sodium monitoring at Day 4 and Day 28 is recommended in males older than 65 years of age at 100 µg. The serum sodium levels at Day 4 and Day 28 should be ≥ 135 mmol/L. In males below 65 years of age who are treated at 100 µg, no further monitoring appears to be warranted. In female subjects who are treated at 25 µg, no further monitoring appears to be warranted.

Dosing

[0149] Results of Study CS29 demonstrated that the 10 µg dose was considered a subtherapeutic dose for the primary efficacy parameters when looking at the overall population. While the 100 µg dose was clearly efficacious, the risk of hyponatraemia was greater than with the lower doses of desmopressin. Although not as effective as the 100 µg dose, the benefit: risk ratio favored the 25 µg and 50 µg doses. The 25 µg dose was clearly less likely to cause hyponatraemia than the 50 µg and 100 µg doses and was statistically significantly superior to placebo in the primary efficacy endpoint among females. Among males, the 100 µg desmopressin dose was statistically significantly superior to placebo for the primary endpoint. Based on these gender differences, the MED for females is 25 µg and the MED for males is 100 µg.

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P A T E N T K R A V

1. Sammensætning omfattende en oralt dispergerbar (ENG: orodispersible) dosis af desmopressin på 25 µg målt som den frie base af desmopressin, til anvendelse til reducere ring af natlige vandladninger hos en kvindelig patient med behov derfor, hvor dosen er til indgivelse til patienten forud for sengetid og reducerer patientens natlige vandladninger sammenlignet med før indgivelse, og hvor den gennemsnitlige reduktion af natlige vandladninger ved uge 52 af indgivelse er øget sammenlignet med den gennemsnitlige reduktion af natlige vandladninger ved dag 28 af indgivelse.
2. Sammensætning til anvendelse ifølge krav 1, hvor dosen af desmopressin fri base er forsynet i form af acetat-saltet af desmopressin.
3. Sammensætning til anvendelse ifølge krav 1, hvor den oralt dispergerbare (ENG: orodispersible) dosis af desmopressin er en doseringsform omfattende desmopressinacetat, gelatine,mannitol og citronsyre.

DRAWINGS

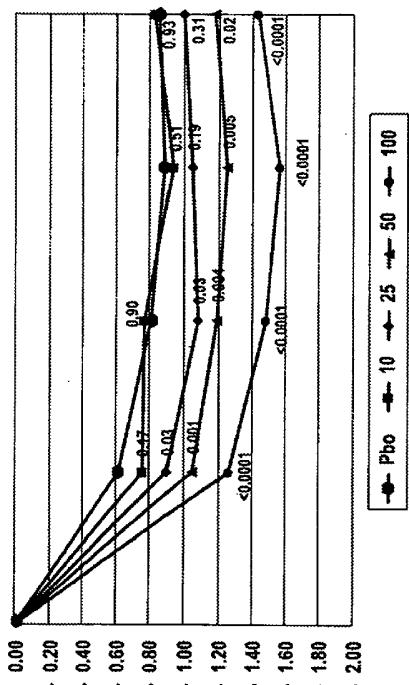
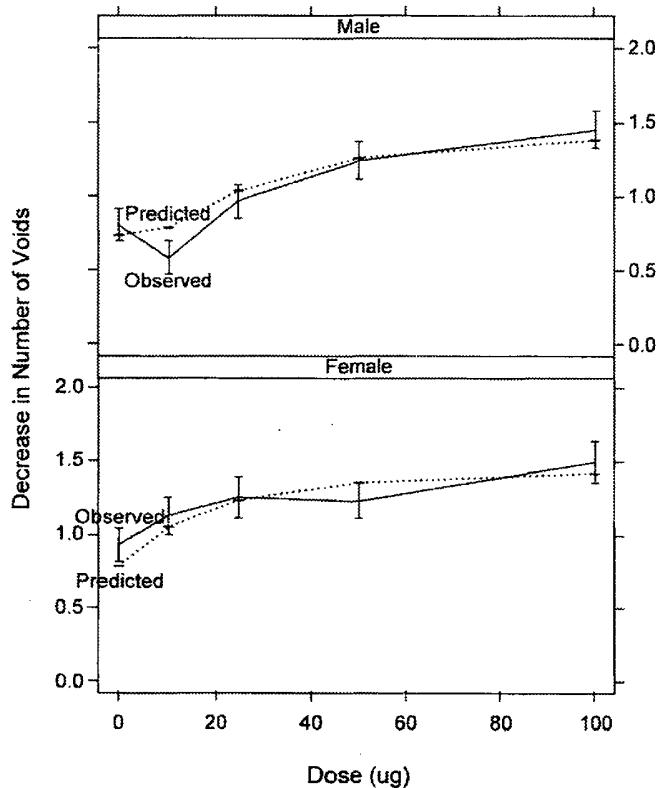


Figure 1

Figure 2

Model Fit by Sex



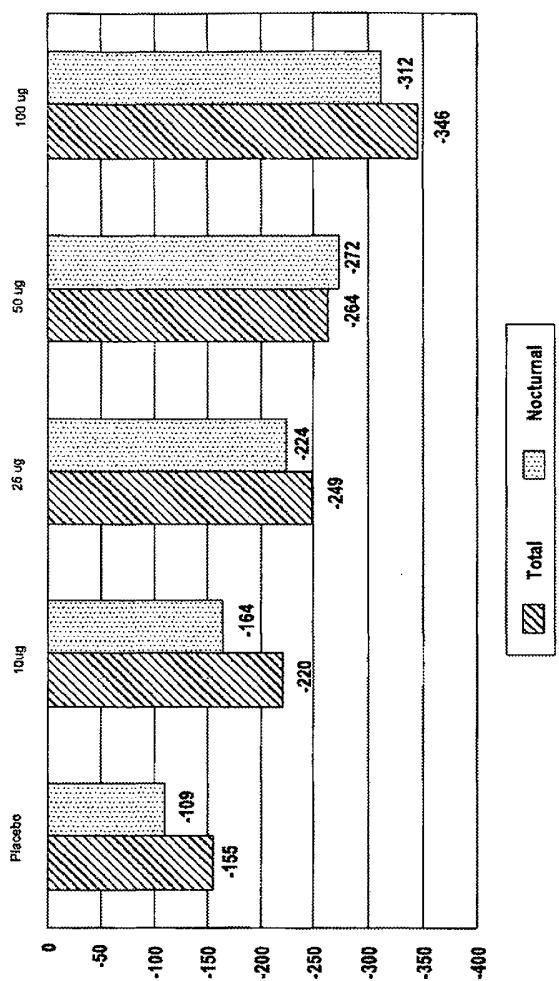


Figure 3

Figure 4