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2 SYNOPSIS

Study identifier MRZ 60201_2069_1

Title of study

Prospective, randomized, double-blind, placebo-controlled, parallel-group, 3-stage dose-finding study to identify a safe and effective dose of NT 201 for unilateral injection into the soft palate for treatment of habitual snoring

Investigator(s), study site(s)

Investigators

Principle Investigator: [redacted]

Sub-investigator: [redacted]

Study site

[redacted]

Germany

Publication (reference)

Not applicable.

Study period First subject enrolled: 30-JAN-2012 **Phase: 2**
Last subject completed: 23-NOV-2012

Objectives

Primary objective(s)

- To identify a safe and effective dose of NT 201 for unilateral injection into the soft palate for the treatment of habitual snoring

Secondary objective(s)

- To evaluate the safety of up to 3 different doses of NT 201 after single unilateral injection into the soft palate for the treatment of habitual snoring

- To evaluate the efficacy of up to 3 different doses of NT 201 after single unilateral injection into the soft palate for the treatment of habitual snoring

Study design and methodology

This was a prospective, randomized, double-blind, placebo-controlled, parallel-group, 3-stage dose-finding study. Subjects with habitual snoring were to be randomized at 3:1 ratio to receive injection of NT 201 or placebo in the soft palate. Dose of NT 201 injection was planned as 2.5 U, 5 U and 7.4 U for three dose stages respectively.

Subjects were scheduled to have 5 visits including the screening visit, the baseline/ injection visit, two follow-up visits after 1 week and 4 weeks of injection and a final visit at 3 months post-injection, when safety and efficacy measurements were to be conducted.

16 subjects were planned for each dosing stage, in total 48 subjects were to be enrolled.

There was a Data Monitoring Committee (DMC) to monitor the overall safety of the study participants and to give recommendations at end of stages 1 and 2 based on the efficacy and safety results.

Due to premature study termination for non-safety reasons dose stage 2 and stage 3 were not investigated. Subjects already randomized for stage 1 completed the study as planned.

Hence, no recommendation regarding continuation for the next higher dose in stage 2 based on efficacy or safety was made by the DMC.

Number and time points of visits

Number and time points of visits were scheduled identical for all of the three dose stages.

Screening visit

Screening visit [V1] (Day -15 to -4)

Baseline/ Injection visit

Baseline visit, also injection visit [V2] (Day -1 to 1): subjects stay overnight (of Day -1) at the investigational site for the acquisition of baseline parameters and inclusion/ exclusion parameters. The next day (Day 1) only eligible subjects were to receive treatment.

Follow-up visits

Follow-up visit 3 [V3] (Day 8±1)

Follow-up visit 4 [V4] (including an overnight observation, Week 4, day 29±3)

Follow-up visit 5 [V5] (including an overnight observation, Week 12, day 85±3)

Number of subjects planned

In total up to 48 subjects were planned, depending on the DMC decision whether the study was to be completed after dosing stage 1, 2 or 3, a total of 16, 32 or 48 subjects were to be enrolled, respectively.

Due to the premature study termination eight subjects were enrolled in the study.

Diagnosis and main criteria for in- and exclusion

Indication

- Habitual snoring

Main inclusion criteria

- Female or male subjects aged 18-70
- Subject suffering from snoring for at least 3 months prior to the study start and seeking for help to treat snoring
- Subject with a peak SI ≥ 15/ h at baseline measured by the acquired snoring sound at baseline visit V2
- Subject who understands the nature of the study and provide written Informed Consent [IC] at screening visit V1

Main exclusion criteria

- Obese subject (Body Mass Index [BMI] ≥ 30)
- Subject with severe obstructive sleep apnea syndrome [OSAS]
- AHI ≥ 10 / h sleep at the baseline visit (V2), measured by WatchPAT
- Subject with an RDI ≥25/ h sleep at the baseline visit (V2), measured by WatchPAT
- Subject who has undergone any Botulinum neurotoxin treatment in the history
- Subject with generalized disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome)
- Acute infections of the pharynx

- Subject with other contraindications to Botulinum neurotoxin according to the current labeling including known hypersensitivity to any of the excipients (human albumin, sucrose)

- Subject who have participated in a previous stage of this study

- Subject with upper respiratory tract pathology as assessed by an ENT specialist

- Subject with deformed finger(s) at the non-dominant hand affecting the fitting of the finger mounted pneu-optical probe to measure the peripheral arterial tone [PAT] signal of the WatchPAT apparatus

- Subject undergoing α-blocker medication or subjects with bilateral sympathectomy, Raynaud disease, acrocyanosis, severe vasculopathy, neuropathy, or autonomic nervous system dysfunction affecting the PAT signal readout based on the α-adrenergic innervations of the smooth muscles of the vasculature of the finger

- Subject with any kind of speech disorder, dysphagia, and / or aspiration in the medical history

- Known alcoholism, drug or medication abuse in the medical history

- Subject with bleeding disorders of any type and / or receiving anticoagulant therapy

- Regular intake or planned onset of hypnotics and sedative medications, e.g. benzodiazepines, chloralhydrate and combinations, barbiturates (except of mild phytotherapeutics, e.g. valerian, hop, and combinations)

- Concomitant intake or onset of the following medication:

    - 4-aminochinolines

    - Aminoglycosides or spectinomycin, or other medical products interfering with neuromuscular transmission, e.g. tubocurarine-type muscle relaxants

    - Daily psychotropic medication

    - Anti-snoring products during the course of study, such as foams, devices

Test product

NT 201 (active ingredient: NT 101, Clostridium botulinum neurotoxin type A [150 kDa], Botulinum neurotoxin type A free from complexing proteins, USAN: incobotulinumtoxinA) powder for solution for injection: one vial contains 50 mouse LD50-units NT 101, sucrose, and human serum albumin. Prior to administration, one vial of NT 201 was reconstituted with sterile physiological (0.9%) sodium chloride. The

reconstitution volume for the three dose stages was 8 ml, 4 ml and 2.7 ml respectively, resulting in the concentration of 6.25 U/ml, 12.5 U/ml and 18.5 U/ml.

Reference product

Placebo

Placebo identical in appearance to the active study medication consisted of sterile physiological (0.9%) sodium chloride. Injected volume is identical to that of the active study medication. Injection site and technique were identical to the active study medication.

Duration of study treatment

The duration of study participation for each subject was up to 14 weeks, consisting of up to two weeks screening period before the injection and 12 weeks observation period following the injection.

Criteria for evaluation

The following evaluations were planned:

Efficacy

Efficacy assessments

- Snoring Index [SI]: number of snoring events per hour of sleep, snoring is defined as events of no less than 40 dB wave pressure of the recorded sound
- Bed partner satisfaction: a 6-point Likert item to rate the global assessment of the treatment by the bed partner
- Loudness: a psychoacoustic measure reflecting the sound quality perceived by human ears (unit is sone, loudness is a psychological correlate of the physical strength of the sound)
- Annoyance: a psychoacoustic measure combining different hearing sensations to estimate the burden of noise to the human auditory system
- Epworth Sleepiness Scale [ESS]: rating of the possibility of daytime sleepiness. 8 items, 4-point Likert-scale
- Bed Partner Questionnaire [BPQ]: assessment of sleeping behavior and snoring perceived by the bed partner of the subject

Pharmacodynamics

Not applicable.

Pharmacokinetics

Not applicable.

Safety

Safety assessments

- Adverse Events [AEs] including AEs of Special Interest [AESIs] and Serious AEs [SAEs]
- Vital signs (heart rate, blood pressure, respiratory rate)
- Electrocardiograph [ECG]
- Respiratory Disturbance Index [RDI]: respiratory events occurring per hour of sleep
- Apnea-Hypopnea Index [AHI]: total number of complete cessations (apnea) and partial obstructions (hypopnea) of breathing occurring per hour of sleep
- Physical examination
- Neurological examination
- Clinical biochemistry, hematology and coagulation
- Alcohol test (breath)
- Urinary screening of sedatives
- Pregnancy test
- Ear-nose-throat [ENT] examination including local injection site control

Statistical methods

For the confirmatory primary analysis the calculation of Hodges Lehmann confidence intervals was planned based on the full analysis set (i.e. all randomized and treated subjects with a baseline and post-baseline evaluation of the Snoring Index). The overall alpha level of 2.5% (one-sided) was to be divided into 0.25% (For primary endpoint of dose 1), 0.5% (For primary endpoint of dose 2) and 1.75% (For primary endpoint of dose 3). For each dose the null hypothesis (The relative change from baseline to week 4 under NT 201 is greater or equal to the change from baseline to week 4 under Placebo, i.e. the relative reduction is smaller under NT 201 compared to Placebo) was to be rejected if the

exact two-sided 100x(1-2α)%-Hodges-Lehmann confidence interval (NT 201 minus placebo) lies below zero.

All other analyses were planned to be performed in an exploratory manner using mainly descriptive methods.

Due to premature study termination only descriptive efficacy analyses were performed, and only for dose stage 1 (2.5 U of NT 201). All analyses were done for the population of randomized subjects who were exposed to study medication at least once (i.e. SES) using observed cases only. Confirmatory analyses were not done any longer. No confidence intervals are presented. The primary efficacy variable is summarized by N, mean, standard deviation, median, minimum and maximum. Secondary and tertiary efficacy variables are listed only.

Interim analysis

Not applicable.

Summary of results

Study subjects

Planned for this study were 48 subjects in total and 16 subjects for each dosing stage,

8 subjects completed the study before premature study termination. 6 of whom were treated with verum and two with placebo. All verum-treated subjects were injected with the first dosing stage, i.e., all have been injected with the 2.5 U of NT 201.

Efficacy results

The small sample size did not allow for any meaningful efficacy conclusions.

Pharmacodynamic results

Not applicable.

Pharmacokinetic results

Not applicable.

Safety results

Limited safety conclusions can be drawn due to the small number of safety data from 8 subjects who completed the study with 2.5 U of NT 201 or placebo injections. No deaths, serious adverse events [SAEs] and AEs leading to withdrawal occurred.

4 subjects in the verum group reported a total of 5 AEs, of which 3 were related (two “increased creatin kinase”, mild; one “worsening of AHI (Apnea-Hypopnea Index) and RDI (Respiratory Disturbance Index)”, moderate), 2 were not related to study drug. In the

placebo group, one AE of moderate severity and related to study drug was reported by the investigator ("worsening of AHI/ RDI").

No clinically relevant findings in laboratory results and vital signs were observed except for the increase of creatin kinase in two verum subjects which were documented as AEs and were evaluated as "related".

Conclusions

The study was designed as prospective, randomized, double-blind, placebo-controlled, parallel-group, 3-stage dose-finding study to identify a safe and effective dose of NT 201 for unilateral injection into the soft palate for treatment of habitual snoring.

This study was terminated on 30-NOV-2012 since there was no prospect of completing the study within a reasonable time although every effort had been taken to identify eligible subjects for this study. The main reason of non-eligibility was obstructive sleep apnea syndrome. Eight subjects in the first dosing group completed the study, 6 of whom had received NT 201 injection and 2 of them had received placebo injection.

The small sample size of eight subjects did not allow for any meaningful efficacy conclusions.

Limited safety conclusions can be drawn due to the small number of safety data from 6 subjects who completed the study with 2.5 U of NT 201 injections. No deaths, serious adverse events [SAEs] and AEs leading to withdrawal occurred. Two AEs were rated as "moderate, related" by the investigator, one in the verum group and one in the placebo group. All other AEs are rated as "mild". There were no safety concerns at any time of the study.

No new safety signals were identified in this study and the safety profile remains still unchanged.