The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: NKP106254
Title : Randomised, double-blind, placebo controlled, cross-over study comparing the effects of both single dose and repeated dosing treatment for 14 days of vestipitant or vestipitant + paroxetine combination in an enriched population of subjects with tinnitus & hearing loss
Rationale: Tinnitus associated with hearing loss is a high prevalence audiologic disorder with important unmet needs as far as therapy is concerned. The present study explored the possible beneficial effects on tinnitus loudness or annoyance of a combination drug treatment aimed to increase the local inhibitory activity of neural circuitries involved in sound perception and generation. Two 14 day treatment conditions, i.e., SSRI paroxetine (20 mg/day) plus the NK1 antagonist vestipitant (25mg /day) or vestipitant alone (25 mg /day), were compared to placebo in patients suffering from tinnitus. Effects on principal endpoints were collected within 4 hrs from last administration. Audiometry and computer-based Automated Psychoacoustics were performed as instrumental endpoints to support subjective scores.
Phase: II
Study Period: 05Dec06 to 06Aug09
Study Design: Randomised, double-blind, placebo controlled, 3 way cross-over study.
Centres: 1 centre in 1 country (UK)
Indication: Tinnitus associated with hearing loss
Treatment: Subjects were randomized to one of the following six repeated dosing treatment sequences in accordance with the randomization schedule produced using validated software (Randall) prior to the start of the study: A/B/C, A/C/B, B/A/C, B/C/A, C/A/B and C/BA Where A represents placebo, B represents Vestipitant alone and C represents the combination between Vestipitant and Paroxetine. The Treatment Phase consisted of three 14-day treatment periods separated by a wash-out interval of 14 days. All subjects received all treatments. Treatments were: placebo, vestipitant 25 mg/day and vestipititant 25 mg/day + paroxetine 20 mg/day.
Objectives: The present study explored the possible beneficial effects on tinnitus loudness, tinnitus subjective features (pitch, intensity, distress, alertness/ anxiety), audiometry, and clinical scores (tinnitus handicap inventory, annoyance of hyperacusis, tinnitus diary, sleep) of a combination drug treatment aimed to increase the local inhibitory activity of neural circuitries involved in sound perception and generation.

Statistical Methods:

Sample Size Considerations: Data for Visual Analogue Scales for Loudness were obtained from Baguley DM *et al*, *Otology and Neurotology*; 2005, 26:169-176. From a re-analysis of these data on 16 subjects, a within-subject standard deviation of VAS change from pre-dose baseline of 12.88 mm was derived. In the same study an effect of about 28 mm was observed for Lidocaine. Assuming that the within subject SD in this study is the same observed in the above reported study and an effect of 14 mm (half of the effect seen for Lidocaine), 19 evaluable subjects would provide a 90% power. Assuming a drop-out rate not greater than 20% led to a sample size of 24 subjects.

VAS tinnitus (intensity, tone, distress) and arousal/anxiety, Tinnitus Handicap Inventory (THI) total score & Tinnitus Aggravation Scores (0-7): For each domain, data were summarized by treatment and time and plotted. For each domain data were analyzed using a mixed effect model including terms for:

- Fixed effects: period, treatment, time point (day 1 2h post dose, day14 pre-dose, day 14 2h post dose), time point*treatment
- Random effects: subject, subject*period.

Treatment means were estimated on each time point and treatment differences were reported with 95% confidence intervals.

Annoyance of Hyperacusis, diary (Tinnitus scores and hyperacusis): Data (mean values over the treatment period for diary data) will be analyzed using a mixed effect model including terms for:

- Fixed effects: period, treatment
- Random effects: subject

Treatment means were estimated and treatment differences were reported with 95% confidence intervals.

Study Population:	
Number of Subjects:	
Planned N	24
Dosed N	24
Completed n (%)	22 (92)
Total Number Subjects Withdrawn N (%)	2 (8)
Withdrawn due to Adverse Events n (%)	2 (8)
Withdrawn due to Lack of Efficacy n (%)	0 (0)
Withdrawn for Other Reasons n (%)	0(0)
Demographics	
N (ITT)	24
Females: Males	6:18
Mean Age in Years (sd)	55.5 (5.7)
Mean Weight in Kg (sd)	81.8 (15.2)
White n (%)	24 (100)

Pharmacokinetics (PK),Pharmacodynamics (PD), PK/PD Endpoints:
PK Results:
No relevant differences in Vestipitant plasma concentrations were observed between the subjects given the combination with Paroxetine and those receiving Vestipitant alone.

Pharmacodynamic Results:
VAS Tinnitus scores (Intensity, tone, distress) No statistically significant treatment effect was detected for any endpoint at any time point. Treatment differences were always negligible and very far from the level of statistical significance
VAS Arousal-Anxiety
No statistically significant treatment effect was detected for any endpoint at any time point. The largest difference, even if not statistically significant, was about a greater level of drowsiness following the 2 active drugs vs placebo.
THI
No statistically significant effect was detected among the active treatments vs placebo at any time point. However at the Day 1 2H time point, the THI total score was lower for Vestipitant + Paroxetine and the difference was statistically significant vs Vestipitant alone. This effect was not confirmed at the other time points.
QIDS-SR
No statistically significant treatment effect was detected. Scores were relatively low (mean values around 4, while the maximum value of the scale is 27) for all the treatments.
Tinnitus Aggravation Score
No statistically significant treatment effect was detected. The largest difference was observed after 2 hours from dosing at Day 1 in the comparison Vestipitant – Placebo. The difference was close to the level of the statistical significance but it wasnt co nfirmed at the other time points.
Annoyance of Hyperacusis
No statistically significant treatment effect was detected. Scores were relatively low (mean values around 1, median values of 0) for all the treatments.
Tinnitus VAS scores (diary –m ean over the treatment period)
A statistically significant worsening of intensity and distress scores were observed after Vestipitant vs placebo.

PK/PD Conclusions:
No specific PK/PD relationships were observed between the primary PD endpoints and Vestipitant plasma concentrations.

Safety results:
The study drug was generally well tolerated. There were no serious adverse events, deaths or pregnancies.

There were two withdrawals due to an adverse event.

- Subject 10 was withdrawn in period 1 (Vestipitant + Paroxetine) after a single dose of study medication due to multiple symptoms (sweating, tremor, dry mouth, anxiety) starting ~2 h post-dose and resolved by ~ 5 h post-dose and which were deemed by the investigator to be due to exacerbation of anxiety..
- Subject 16 withdrew in period 3 (Vestipitant), towards end of treatment (79d), due to worsening of tinnitus. Treatment blinds were not broken

Though the frequency of adverse events was generally similar across the three treatment periods, the frequency was slightly higher for the combination of vestipitant + paroxetine (88%) than for either vestipitant (70%) or placebo (61%) alone. The most common adverse events belonged to the nervous system disorders (headache, somnolence & dizziness) and gastrointestinal system disorders (nausea & dyspepsia) groups. There were no clinically significant laboratory abnormalities or changes from baseline. There were no clinically significant ECG findings, QT changes, or clinically significant vital sign changes.

Any Adverse Events:			
N (ITT)	24		
No. subjects with AEs n (%)	23 (96)		
Most Frequent AEs (≥ 3 subjects in any treatment group)	**Placebo**	**Vestipitant**	**Vestipitant + Paroxetine**
Nervous System Disorders:			
Any Event	11 (48)	11 (48)	16 (67)
Headache	10 (43)	8 (35)	12 (50)
Dizziness	1 (4)	3 (13)	6 (25)
Somnolence	0	1 (4)	5 (21)
Balance Disorder	0	0	4 (17)
Lethargy	1 (4)	0	3 (13)
Gastrointestinal Disorders:			
Any Event	6 (26)	6 (26)	10 (42)
Nausea	3 (13)	1 (4)	6 (25)
Psychiatric Disorders:			
Any Event	3 (13)	5 (22)	9 (38)
Depression	1 (4)	3 (13)	1 (4)
Insomnia	0	2 (9)	3 (13)
Ear and Labyrinth Disorders			
Any Event	2 (9)	5 (22)	6 (25)
Tinnitus	0	4 (17)	3 (13)
General Disorders and Adminstration Site Conditions:	2 (9)	4 (17)	9 (38)
Any Event	1 (4)	4 (17)	5 (21)
Fatigue	1 (4)	0	4 (17)
Feeling Abnormal			
Musculoskeletal and Connective Tissue Disorders: Any Event	3 (13)	4 (17)	3 (13)
Respiratory, Thoracic and Mediastinal Disorders:	0	1 (4)	6 (25)
Any Event	0	1 (4)	3 (13)
Oropharyngeal Pain			
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: There were no serious adverse events, deaths or pregnancies.			
Publications: None at the time of this report.			