Study No: SPE111155

Title : A double blind, parallel group, placebo controlled study to evaluate the effect of a single oral dose of GSK958108 on ejaculatory latency time (ELT) in male patients suffering from premature ejaculation.

Rationale: GSK958108 is a 5HT1A receptor antagonist, which is being investigated by GSK for the treatment of primary premature ejaculation. The purpose of this double blind, parallel group, and placebo controlled masturbation model study was to evaluate the effect of a single oral dose of GSK958108 on ejaculatory latency time (ELT) in male subjects suffering from premature ejaculation (PE).

Phase: I

Study Period: 26 NOV 2008 to 11 DEC 2009

Study Design: This was a two part, double blind, parallel group, placebo controlled study.

Centres: One centre in Italy.

Indication: Pre-mature ejaculation

Treatment: In the first part, 20 male PE subjects were enrolled and randomised to receive either GSK958108 3 mg or placebo in a 1:1 ratio, in accordance with the randomisation schedule.
In the second part, 15 male PE subjects were enrolled and randomised to receive either placebo or GSK958108 7 mg in a 1:2 ratio, in accordance with the randomisation schedule.

Objectives: The primary objective was to evaluate the effect of a single oral dose of GSK958108, on ejaculatory latency time (ELT) as measured in the masturbation model.

Statistical Methods:

Sample Size Considerations

Sample size for this study was based on feasibility.

Sample Size Assumptions

Based on a between subject CV of 49%, with a sample size of 10 subjects per group, it was estimated that the lower and upper limits of the 95% confidence interval (CI) for the ratio of geometric means of ELT (GSK958108:placebo) would be obtained by dividing/multiplying the point estimate of the ratio by 1.54. For example, if the point estimate of the ratio of geometric means was 1.0, or 2.0, then 95% CI would be approximately (0.65, 1.54), or (1.30, 3.07), respectively.

Sample Size Sensitivity

Based on a between subject CV of 68%, with a sample size of 10 subjects per group, it was estimated that the lower and upper limits of the 95% CI for the ratio of geometric means of ELT (GSK958108:placebo) would be obtained by dividing/multiplying the point estimate of the ratio by 1.77. For example, if the point estimate of the ratio of geometric means was 1.0, or 2.0, then 95% CI would be approximately (0.57, 1.77), or (1.13, 3.53), respectively.

Interim Analyses

An analysis on the primary ELT endpoint was performed in advance of the full database freeze (DBF) but after all initial planned 20 subjects had been dosed. Following these results, the protocol was amended to include an additional dose arm and a further 15 subjects were enrolled.
Summary statistics of ELT results by treatment and the summary of results of statistical analysis of change in ELT by treatment were presented. Results were presented at the treatment group level only.
The reporting of all other data was performed after the database had been frozen and unblinded.

Final Analyses

The final planned analysis was performed after all subjects completed the study and after DBF.
The programs for tables, figures and listings were developed using SAS version 9.1.3 on a UNIX platform and then loaded into Harmonisation and reporting programme (HARP) (the GSK reporting tool) once final. The final output was then produced by running the programs in HARP.

Safety:

All safety data of potential clinical importance were listed. Adverse events, laboratory test, ECGs, vital signs and eye examination tests were summarised.

Pharmacodynamic:

Data displays from the PD analyses were presented for 2 separate subgroups:

- Statistical analysis was performed upon completion of the initial 20 subjects in the study, 10 subjects randomised to receive GSK958108 3 mg and 10 subjects randomised to receive placebo.
- A further analysis was performed upon completion of the study, pooling all subjects: 10 subjects randomised to receive GSK958108 3 mg, 10 subjects randomised to receive GSK958108 7 mg, and 15 subjects randomised to receive placebo.

The ratio ELT : baseline was log-transformed and analysed using Analysis of Covariance, with log (baseline) and treatment as fixed effects. Point and 95% interval estimates of the difference in least-squares means of the log-transformed ratio post : pre-treatment ELT (GSK958108-placebo) were derived. These estimates were exponentiated

(back-transformed) to express point and interval estimates on a ratio scale. The final estimates therefore represent the ratio of the geometric means for the ratio post: pre-treatment ELT (GSK958108:placebo). A jacknife analysis was performed and results presented graphically.
A boxplot of ELT was produced by treatment. Kaplan-Meier plots of pre-dose and post-dose ELT were also provided.

Changes in conduct of the study or planned analyses

Following results of the primary ELT endpoint in advance of DBF from the initial 20 subjects which had completed the study, the protocol was amended in order to add an additional dose arm. A further 15 subjects were enrolled, 10 subjects randomised to receive GSK958108 7 mg and 5 subjects randomised to receive placebo.
The planned analysis specified in the RAP for the primary ELT analysis was to analyse log-transformed ELT. Instead, the log-transformed ratio ELT : baseline was analysed. The interpretation of the geometric least square means differs with these 2 approaches but the estimated back-transformed geometric mean ratios are equivalent.
Data did not permit pharmacokinetic parameters AUC(0-∞) and t½ to be derived, due to the short blood sampling period.

Study Population: Heterosexual male subjects with long term symptoms of PE that meet diagnostic and statistical manual of mental disorder (DSM)-IV-TR criteria for PE, aged between 18 and 50 years with body weight ≥50 kg (110 lbs) and body mass index (BMI) within the range 19.0 – 29.9 kg/m^2 inclusive) were enrolled in this study.

	Placebo	GSK958108		Total
Number of Subjects:		**3 mg**	**7 mg**	
Planned N	15	10	10	35
Dosed N	15	10	10	35
Completed n (%)	15 (100)	10 (100)	10 (100)	35 (100)
Total Number Subjects Withdrawn N (%)	0	0	0	0
Withdrawn due to Adverse Events n (%)	0	0	0	0
Withdrawn due to Lack of Efficacy n (%)	0	0	0	0
Withdrawn for Other Reasons n (%)	0	0	0	0
Demographics				
N	15	10	10	35
Females: Males	0:15	0:15	0:15	0:15
Mean Age in Years (sd)	40.9 (6.20)	38.3 (3.74)	44.7 (3.65)	41.2 (5.40)
Mean Weight in Kg (sd)	79.1 (8.65)	79.2 (7.62)	75.4 (8.53)	78.1 (8.28)
White n (%)	15 (100)	10 (100)	10 (100)	35 (100)

Pharmacokinetics (PK): A summary of **s**elected PK parameters is given in table below:

PK parameters	**GSK958108 Single Dose**	
	3 mg	**7 mg**
	N=10	**N=10**
t_{max} (h)[1]	4.5 (3.0-4.5)	4.5 (3.0-4.5)
C_{max} (ng/mL)[2]	3.84 (37)	18.1 (40)
AUC(0–30) (ng.h/mL)[2]	54.3 (32)	234.0 (22)
AUC(0–24) (ng.h/mL)[2]	47.4 (32)	204 (25)

1. Median (range).
2. Geometric mean (CVb%)

Pharmacodynamics (PD): The results of the statistical analysis of ELT are presented in the table below

Population subgroup	**Comparison**	**Geom. Mean**		**Ratio**	**95% CI for ratio**
		Test (post : pre-trt)	**Ref (post : pre-trt)**		
All Subjects (n=35)[1]	GSK958108 3 mg:Placebo	1.542	1.328	1.16	(0.84, 1.61)
	GSK958108 7 mg:Placebo	2.346	1.328	1.77	(1.28, 2.44)
Part 1 (n=20)	GSK958108 3 mg:Placebo	1.554	1.177	1.32	(0.93, 1.87)
Part 2 (n=15)	GSK958108 7 mg: Placebo	2.364	1.642	1.44	(0.87, 2.39)

1. %CVb was estimated as 40.5% in primary analysis.

PK/PD Endpoints: A summary of NONMEM PK-PD model parameters (mean±SEM) is given the table below:

Model/ Exposure metrics	**Baseline (sec)**	**$\eta_{baseline}$ (CV%)**	**Slope (sec/unit of metrics)**	**η_{slope} (CV%)**	**Residual error (CV%)**	**ΔOBJ vs. basal model**	**notes**
Basal	95.5±11.1	79.4±30.9	NA	NA	41.5±16.6	0	

Linear C_{max}	79.0±8.96	76.1±26.6	5.67±1.40	107.9±55.8	55.0±20.5	-29.717	+2 param
Linear $C_{3.5h}$	79.0±8.97	75.9±26.4	6.33±1.60	112.9±59.2	55.1±20.5	-28.929	+2 param
Linear Cmax/tmax	83.6±9.76	86.4±29.9	16.1±5.7	0 FIX	61.3±19.9	-24.060	+1 param
Linear AUC(0-3.5)	79.2±8.98	75.2±26.0	2.93±0.79	122.3±60.5	55.3±20.4	-27.806	+2 param

Safety results: A total of 23 AEs reported by 16 subjects in this study. Out of these AEs, 2 AEs were pre-treatment AEs. Headache was the most common AE reported predominantly with placebo. Somnolence was the most common AE with GSK958108 during the study. None of the subject was withdrawn from the study due to AEs. There were no clinically significant abnormal findings from the eye examination. There were no clinically significant changes in vital signs, ECGs or laboratory parameters.

Adverse Events:	**Placebo**	**GSK958108**		**Total**
		3 mg	**7 mg**	
N	N=15	N=10	N=10	N=35
No. subjects with AEs n (%)	7 (47)	3 (30)	6 (60)	16 (46)
All AEs, n(%)				
Headache	5 (33)	0	2 (20)	7 (20)
Somnolence	0	0	3 (30)	3 (9)
Back pain	0	1 (10)	1 (10)	2 (6)
Neck pain	1 (7)	0	1 (10)	2 (6)
Tinnitus	0	0	2 (20)	2 (6)
Oropharyangeal discomfort	0	0	1 (10)	1 (3)
Oropharyangeal Pain	0	1 (10)	0	1 (3)
Nausea	1 (7)	0	0	1 (3)
Vomiting	1 (7)	0	0	1 (3)
Cystitis	0	1 (10)	0	1 (3)

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: There were no deaths or non-fatal SAEs were reported in this study.