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GENERIC DRUG NAME and/or COMPOUND NUMBER: Gisadenafil Besylate / UK-369,003

PROTOCOL NO.: A3711030

PROTOCOL TITLE: A Double-Blind, Placebo Controlled, Parallel Group, Multicentre Study to Assess the Duration of Action, Safety and Toleration of Differing Doses and Combinations of Immediate and Modified Release Formulations of UK-369,003 and Cialis Compared to Placebo in Adult Male Subjects With Erectile Dysfunction

Study Centers: A total of 30 centers took part in the study and randomized subjects: 5 each in Australia and Germany, 4 each in Canada and France, 3 each in Belgium, Netherlands, Spain and the United Kingdom.

Study Initiation and Final Completion Dates: 02 February 2005 to 24 June 2005

Phase of Development: Phase 2

Study Objectives:

Primary Objective: To examine the efficacy in outpatients with erectile dysfunction of a combination of immediate release (IR) and modified release (MR) gisadenafil besylate and the approved Type 5 phosphodiesterase (PDE5) inhibitor Cialis taken orally between 12 and 16 hours prior to sexual activity over a 4-week treatment period compared with placebo.

Secondary Objective: To assess the safety and toleration of a minimum of 4, and a maximum of 14, doses of IR and MR oral gisadenafil besylate taken as required over a 4-week treatment period.

METHODS

Study Design: This was a phase 2 multicenter, double-blind, placebo controlled, parallel group study in adult males with erectile dysfunction. Subjects had 4 visits: screening, baseline (randomization) and after 2 and 4 weeks (end of treatment [EOT]). The screening visit was followed by a 4-week washout period. Subjects also had a follow up visit either in the clinic or by telephone contact 7 days after the end of the study to assess any adverse events (AEs) following drug discontinuation. The timetable of study procedures is summarized in Table 1.

Table 1. Timetable of Study Procedures

Protocol Activities and Forms to be Completed	Screening Visit 1	Rand Visit 2	Treatment Visits Visit 3	Early Discontinuation Visit[a]	End of Treatment Visit 4	Follow-Up[b] Visit 5
Informed consent	X					
Demographics and medical history	X					
Physical examination	X			X	X	X
Inclusion/exclusion criteria	X					
Hematology	X			X	X	X
Blood chemistry	X			X	X	X
Urine dipstick	X			X	X	X
Urinalysis if dipstick positive	X			X	X	X
Sitting and standing blood pressure and pulse rate	X			X	X	X
12-lead supine electrocardiogram	X					
Subject event log		X	X	X	X	
International Index of Erectile Function		X			X	
Erectile Function Domain Score		X			X	
Global Efficacy Questions				X	X	
Quality of Erection Questionnaire		X			X	
Assess adverse events		X	X	X	X	X
Record concomitant medications and non drug treatment and procedures	X	X	X	X	X	X
Dispense trial medications		X				
Collect trial medications			X	X	X	
Subject event log instructions		X	X			
Schedule next visit/telephone contact	X	X	X		X	

Rand = randomization.

a. Subjects who terminated the study early had tests and examinations deemed clinically indicated by the Investigator.

b. All subjects received a telephone call. Those with drug related adverse events had an office visit and may have required laboratory tests and/or a focused physical exam.

Number of Subjects (Planned and Analyzed): It was planned to randomize 335 male subjects (allowing for 25% drop-out rate) to ensure 50 completers per treatment arm. A total of 366 subjects were screened, out of which 335 were randomized to treatment. The sample size was based on the primary efficacy endpoint; the percentage of successful erections between 12 and 16 hours post dose. A sample size of 50 subjects per treatment group was sufficient to detect a difference of 30% between active treatment and placebo, where the placebo response was anticipated as being between 25% and 30%.

Diagnosis and Main Criteria for Inclusion: Subjects were males aged 18-65 years in a stable heterosexual relationship for at least 6 months with documented clinical diagnosis of erectile dysfunction (ED) of at least 6 months duration. All subjects had to have been successfully treated with a PDE5 inhibitor prior to entry into the study. Subjects who were on α-blockers and nitrates were excluded from the study.

Study Treatment: Subjects received gisadenafil besylate 30 mg IR, gisadenafil besylate 15 mg IR + 50 mg MR, gisadenafil besylate 30 mg IR + 100 mg MR tablets, Cialis 20 mg or placebo capsules. Study drug was taken orally 12-16 hours prior to sexual activity. Subjects took 1 dose in any 1 calendar day at a minimum interval of 48 hours apart. Subjects took a minimum of 4 and a maximum of 14 doses over a period of 4 weeks.

Efficacy Endpoints:

Primary Endpoints: The primary endpoint was the proportion of responders based on successful erections hard enough to attempt sexual intercourse that occured within the time period 12-16 hours postdose within each treatment group (as measured by Question 5 in the event log). A subject was a responder if the proportion of times that he achieved a successful erection (out of the number of times he attempted sexual activity) during the 4-week treatment period was ≥25%. The subject event log captured information on sexual activity every time the subject had taken study drug during the 4-week treatment period and the data was used to calculate the proportions.

Secondary Endpoints:

- Proportion of responders based on successful intercourses between 12 and 16 hours post dose (Derived by Question 7 from the subject event log);
- International Index of Erectile Function (IIEF): Question 3 and 4, as well as the scores on the Erectile Function (EF) domain, the Orgasmic function domain, the Sexual desire domain, the Intercourse satisfaction domain and the Overall satisfaction domain;
- Global Efficacy Questions (GEQs);
- Quality of erection as measured by the Quality of Erection Questionnaire (QEQ) total score.

Safety Evaluations: Safety evaluations (clinical monitoring, physical examinations, vital signs, blood pressure and pulse rate, AEs and safety laboratory tests) were carried out at Screening and at the EOT or early discontinuation visits and at the Follow-Up visit if required. Electrocardiograms (ECGs) were recorded at Screening only.

Statistical Methods: The study included the following analysis sets:

Full Analysis Set (FAS) consisting of subjects who had:

- Been randomized to study treatment;
- Received at least 1 dose of study medication;
- At least 1 efficacy assessment (from the IIEF, subject event log or QEQ).

All endpoints, both primary and secondary were analyzed in this population.

Per Protocol Analysis Set (PPAS) consisting of subjects who fulfilled the criteria for inclusion in the restricted FAS, but who in addition, had:

- Completed 4 weeks of study treatment;
- Provided valid baseline data, i.e. IIEF /QEQ baseline data were collected at 28±2 days after screening visit to ensure a 4-week wash-out period (subjects were included when the medication taken records show the date of the last dose of PDE5i medication at 28±2 days before randomization, although, for them, the period between screening and randomization visit might be shorter than 26 days);
- Not failed any inclusion or exclusion criteria that could influence the outcome of the primary efficacy endpoint (discovered subsequent to entering the study);
- Not violated the study specified methodology, or deviated from the study specified methodology, in such a way that could influence the outcome of the primary efficacy endpoint.

Safety Analysis Set: included all subjects who received at least 1 dose of study drug.

Other Analysis Sets:

Restricted Full Analysis Set (RFAS): included subjects from the FAS who additionally had taken at least 4 doses of study drug on separate occasions as captured in the subject event log.

The primary endpoint was analyzed by a logistic regression model for a binary variable, where the model included treatment, and baseline EF score derived from IIEF as a replacement for the baseline of the primary endpoint (which was not collected). The primary analysis was based on the FAS.

A logistic regression model for a binary variable was applied to analyse the proportion of good responders based on successful erections, proportion of responders based on successful intercourses between 12 and 16 hours post dose, and dichotomised GEQ Questions 1 and 2. The model included treatment, and baseline EF score as a replacement for the baseline of the endpoint (which was not collected). Scores of IIEF Questions 3, 4 and the EF domain score and overall score on the QEQ were analyzed using analysis of covariance (ANCOVA), where the model included treatment, and the appropriate baseline measurement.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 2.

Table 2. Subject Disposition

Number of Subjects (%)	Gisadenafil Besylate 30 mg IR	Gisadenafil Besylate15mg IR + 50 mg MR	Gisadenafil Besylate 30mg IR + 100 mg MR	Cialis 20 mg	Placebo

Screened 366					
Assigned to treatment: 335					
Treated	65	67	69	68	66
Completed	56 (86.2%)	62 (92.5%)	65 (94.2%)	66 (97.1%)	62 (93.9%)
Discontinued	9 (13.8)	5 (7.5%)	4 (5.8%)	2 (2.9%)	4 (6.1%)
Analyzed for efficacy					
FAS	65 (100%)	67 (100%)	69 (100%)	68 (100%)	66 (100%)
RFAS	57 (87.7%)	60 (89.6%)	63 (91.3%)	63 (92.6%)	64 (97.0%)
PPAS	48 (73.8%)	47 (70.1%)	50 (72.5%)	55 (80.9%)	55 (83.3%)
Analyzed for safety					
Adverse events	65 (100%)	67 (100%)	69 (100%)	68 (100%)	66 (100%)
Laboratory data	63 (96.9%)	66 (98.5%)	68 (98.6%)	65 (95.6%)	63 (95.5%)
Vital signs	65 (100%)	67 (100%)	69 (100%)	68 (100%)	66 (100%)

FAS = full analysis set; IR = immediate release; MR = modified release; PPAS = per protocol analysis set; RFAS = restricted full analysis set.

All subjects had a primary diagnosis of ED. The mean durations of ED since first diagnosis were similar for all treatment groups. Individual durations ranged between 0.7 and 35 years. Mean ages were similar for all treatment groups. Overall ages ranged between 23 and 65 years. Subject's demographic characteristics are summarized in Table 3.

Table 3. Demographic Characteristics

	Gisadenafil Besylate 30 mg IR (N=65)	**Gisadenafil Besylate 15 mg IR + 50 mg MR (N=67)**	**Gisadenafil Besylate 30 mg IR + 100mg MR (N=69)**	**Cialis 20 mg (N=68)**	**Placebo (N=66)**
Age (years)					
Mean (SD)	54.0 (7.2)	53.4 (8.7)	54.5 (7.6)	54.5 (9.2)	54.2 (8.5)
Range	34-65	31-65	24-65	23-65	26-65
Race					
White	63 (96.9%)	66 (98.5%)	68 (98.6%)	66 (97.1%)	64 (97.0%)
Black	0	0	1 (1.4%)	1 (1.5%)	2 (3.0%)
Asian	1 (1.5%)	0	0	0	0
Other	1 (1.5%)	1 (1.5%)	0	1 (1.5%)	0
Weight (kg)					
Mean (SD)	86.0 (14.7)	88.1 (13.6)[a]	86.3 (15.1)	85.6 (14.7)	88.7 (16.5)
Range	50.0-120.0	65.0-133.0[a]	53.0-175.0	54.0-117.0	48.0-129.0

IR = immediate release; MR = modified release; N = number of subjects; SD = standard deviation.
a. N=66.

Efficacy Results:

Primary Endpoint: For the primary endpoint the comparisons between all active treatments and placebo (Table 4) were statistically significant at the 5% level for the FAS. At both Weeks 2 and 4, 30 mg IR had the highest proportion of responders across the gisadenafil besylate treatment groups while Cialis 20 mg showed the highest proportion of responders among all the treatment groups at Week 4. The results for the RFAS and PPAS were consistent with the FAS.

Table 4. Summary Statistics and Statistical Analysis for the Proportion of Responders Based on Successful Erections Between 12 and 16 Hours PostDose (FAS)

	Gisadenafil Besylate 30 mg IR (N=62)	Gisadenafil Besylate15 mg IR + 50 mg MR (N=65)	Gisadenafil Besylate 30 mg IR + 100 mg MR (N=68)	Cialis 20 mg (N=66)	Placebo (N=65)
Visit 3 (Week 2)	52 (83.9%)	46 (70.8%)	43 (63.2%)	53 (80.3%)	28 (43.1%)
Visit 4 (Week 4/EOT)	52 (83.9%)	49 (75.4%)	49 (72.1%)	57 (86.4%)	32 (49.2%)
Statistical analysis					
Observed proportion	0.84	0.75	0.72	0.86	0.49
Estimated proportion	0.84	0.76	0.73	0.87	0.50
Odds ratio vs placebo (95% CI)	5.45 (2.40, 13.3)	3.20 (1.52, 6.98)	2.80 (1.35, 5.95)	7.02 (3.03, 17.7)	-
p-value	<0.001	0.003	0.006	<0.001	-

CI = confidence interval; EOT = end of treatment; FAS = full analysis set; IR = immediate release; MR = modified release; N = number of subjects; vs = versus.

Secondary Endpoints:

The Response Rate for Good Responders Based on the Proportion of Successful Erections – FAS: For the proportion of good responders based on successful erection between 12 and 16 hours postdose, the differences from placebo were statistically significant at the 5% level. Gisadenafil besylate 30 mg IR showed the highest proportion of responders among all gisadenafil besylate treatment groups, and a higher proportion of responders than Cialis.

Summary statistics at Weeks 2 and 4 and statistical analysis at Week 4 for the proportion of good responders based on successful erections between 12 and 16 hours postdose are presented in Table 5 for the FAS.

Table 5. Summary Statistics and Statistical Analysis for the Proportion of Good Responders Based on Successful Erections Between 12 and 16 Hours PostDose (FAS)

	Gisadenafil Besylate 30 mg IR (N=62)	Gisadenafil Besylate 15 mg IR + 50 mg MR (N=65)	Gisadenafil Besylate 30 mg IR + 100 mg MR (N=68)	Cialis 20 mg (N=66)	Placebo (N=65)
Visit 3 (Week-2)	46 (74.2%)	31 (47.7%)	33 (48.5%)	45 (68.2%)	13 (20.0%)
Visit 4 (Week-4/EOT)	41 (66.1%)	27 (41.5%)	28 (41.2%)	42 (63.6%)	15 (23.1%)
Observed proportion	0.66	0.42	0.41	0.64	0.23
Estimated proportion	0.66	0.41	0.41	0.63	0.23
Odds ratio vs placebo	6.49	2.36	2.36	5.83	-
(95% CI)	(3.02, 14.6)	(1.11, 5.16)	(1.12, 5.13)	(2.75, 12.9)	
p-value	<0.001	0.027	0.026	<0.001	-

CI = confidence interval; EOT = end of treatment; FAS = full analysis set; IR = immediate release; MR = modified release; N = number of subjects; vs = versus.

Summary statistics at Weeks 2 and 4 and statistical analysis at Week 4 for the proportion of responders, based on successful intercourse between 12 and 16 hours postdose, are presented in Table 6 for the FAS.

Table 6. Summary Statistics and Statistical Analysis for the Proportion of Good Responders Based on Successful Intercourse Between 12 and 16 Hours PostDose (FAS)

	Gisadenafil Besylate 30 mg IR (N=62)	Gisadenafil Besylate 15 mg IR + 50 mg MR (N=65)	Gisadenafil Besylate 30 mg IR + 100 mg MR (N=68)	Cialis 20 mg (N=66)	Placebo (N=65)
Visit 3 (Wk 2)	41 (66.1%)	35 (53.9%)	34 (50.0%)	45 (68.2%)	13 (20.0%)
Visit 4 (Wk 4/EOT)	38 (61.3%)	33 (50.8%)	35 (51.5%)	49 (74.2%)	14 (21.5%)
Observed proportion	0.61	0.51	0.51	0.74	0.22
Estimated proportion	0.61	0.51	0.52	0.74	0.21
Odds ratio vs placebo (95% CI)	5.77 (2.68, 13.0)	3.78 (1.78, 8.38)	3.97 (1.88, 8.76)	10.79 (4.88, 25.3)	-
p-value	<0.001	<0.001	<0.001	<0.001	-

CI = confidence interval; EOT = end of treatment; FAS = full analysis set; IR = immediate release; MR = modified release; N = number of subjects; vs = versus; Wk = week.

IIEF Questions 3 and 4: For IIEF Questions 3 and 4, all treatment differences from placebo were statistically significant at the 5% level. Across gisadenafil besylate treatment groups, 30 mg IR + 100 mg MR produced the greatest numerical increase from Baseline in the scores while Cialis 20 mg showed the greatest numerical increase among all treatment groups.

Summary statistics at Baseline and Week 4 and statistical analysis at Week 4 are presented in Table 7 for the FAS.

Table 7. Summary Statistics for Questions 3 and 4 from the IIEF (FAS)

Question 3 Mean (SE)	Gisadenafil Besylate 30 mg IR (N=59)	Gisadenafil Besylate 15 mg IR + 50 mg MR (N=62)	Gisadenafil Besylate 30 mg IR + 100 mg MR (N=66)	Cialis 20 mg (N=66)	Placebo (N=62)
Baseline	2.3 (0.16)	2.3 (0.15)	2.3 (0.16)	2.1 (0.16)	2.4 (0.16)
Visit 4 (Week 4/EOT)	4.1 (0.16)	4.1 (0.15)	4.2 (0.15)	4.4 (0.11)	2.7 (0.20)
Estimated difference vs placebo (95% CI)	1.45 (1.03, 1.87)	1.46 (1.04, 1.87)	1.57 (1.16, 1.97)	1.82 (1.41, 2.23)	-
p-value	<0.001	<0.001	<0.001	<0.001	-
Question 4 Mean (SE)					
Baseline	2.2 (0.16)	1.9 (0.14)	2.0 (0.15)	1.9 (0.15)	2.1 (0.15)
Visit 4 (Week 4/EOT)	3.8 (0.17)	4.0 (0.17)	4.1 (0.15)	4.4 (0.12)	2.3 (0.18)
Estimated difference vs placebo (95% CI)	1.45 (1.00, 1.90)	1.74 (1.30, 2.18)	1.81 (1.38, 2.25)	2.12 (1.68, 2.56)	-
p-value	<0.001	<0.001	<0.001	<0.001	-

Question 3: Frequency of penetration, Question 4: Maintenance of erection.
CI = confidence interval; EOT = end of treatment; FAS = full analysis set; IIEF = International Index of Erectile Function; IR = immediate release; MR = modified release; N = number of subjects; SE = standard error; vs = versus.

IIEF EF Score: For the EF score from the IIEF (Table 8), all treatment differences from placebo were statistically significant at the 5% level. Across gisadenafil besylate treatment groups, 30 mg IR + 100 mg MR produced the greatest numerical increase from Baseline in

the scores while Cialis 20 mg showed the greatest numerical increase among all treatment groups.

Table 8. Summary Statistics for the IIEF EF Score (FAS)

Mean (SE)	Gisadenafil Besylate 30 mg IR (N=59)	Gisadenafil Besylate 15 mg IR + 50 mg MR (N=62)	Gisadenafil Besylate 30 mg IR + 100 mg MR (N=66)	Cialis 20 mg (N=66)	Placebo (N=62)
Baseline	13.3 (0.70)	13.1 (0.64)	12.6 (0.71)	12.3 (0.77)	12.8 (0.74)
Visit 4 (Week 4/EOT)	22.9 (0.84)	23.5 (0.84)	24.0 (0.83)	25.5 (0.63)	14.9 (0.97)
Estimated difference vs placebo (95% CI)	7.87 (5.61,10.1)	8.49 (6.26,10.7)	9.19 (7.00,11.4)	10.7 (8.46,12.9)	-
p-value	<0.001	<0.001	<0.001	<0.001	-

CI = confidence interval; EOT = end of treatment; EF = Erectile function; FAS = full analysis set; IIEF = International Index of Erectile Function; IR = immediate release; MR = modified release; N = number of subjects; SE = standard error; vs = versus.

Global Efficacy Questions 1 and 2 (GEQs): For both GEQ questions (Table 9), all treatment differences from placebo were statistically significant at the 5% level. Across gisadenafil besylate treatment groups, 30 mg IR + 100 mg MR had the greatest proportion of subjects answering "at least slightly better" on both questions while Cialis 20 mg had the greatest proportion among all treatment groups.

Table 9. Summary Statistics and Statistical Analysis for the Proportion of Subjects Answering at least Slightly Better on GEQ Questions 1 and 2 (FAS)

Question 1 Mean (SE)	Gisadenafil Besylate 30 mg IR (N=60)	Gisadenafil Besylate 15 mg IR + 50 mg MR (N=65)	Gisadenafil Besylate 30 mg IR + 100 mg MR (N=67)	Cialis 20 mg (N=66)	Placebo (N=63)
Observed proportion	0.73	0.78	0.85	0.91	0.17
Estimated proportion	0.73	0.78	0.85	0.91	0.17
Odds ratio vs placebo(95% CI)	13.0 (5.65, 32.3)	17.3 (7.43, 43.6)	27.4 (11.2, 73.9)	47.3 (17.5, 150)	-
p-value	<0.001	<0.001	<0.001	<0.001	-
Question 2 Mean (SE)	**Gisadenafil Besylate 30 mg IR (N=60)**	**Gisadenafil Besylate 15 mg IR + 50 mg MR (N=65)**	**Gisadenafil Besylate 30 mg IR + 100 mg MR (N=67)**	**Cialis 20 mg (N=66)**	**Placebo (N=63)**
Observed proportion	0.75	0.77	0.85	0.88	0.17
Estimated proportion	0.75	0.77	0.85	0.88	0.17
Odds ratio vs placebo (95% CI)	14.2 (6.11, 35.5)	15.8 (6.84, 39.3)	27.1 (11.1, 73.0)	33.9 (13.3, 97.1)	-
p-value	<0.001	<0.001	<0.001	<0.001	-

Question 1: Did treatment affect quality of your erection; Question 2: Did the treatment affect hardness of your erection. CI = confidence interval; FAS = full analysis set; GEQ = global efficacy question; IR = immediate release; MR = modified release; N = number of subjects; SE = standard error; vs = versus.

Overall QEQ Score: For the overall QEQ score (Table 10), all treatment differences from placebo were statistically significant at the 5% level. Across gisadenafil besylate treatment groups, 30 mg IR + 100 mg MR produced the greatest numerical increase in the scores while Cialis 20 mg showed the greatest numerical increase among all treatment groups.

Table 10. Summary Statistics for the Overall QEQ Score (FAS)

Mean (SE)	Gisadenafil Besylate 30 mg IR (N=60)	Gisadenafil Besylate 15 mg IR + 50 mg MR (N=62)	Gisadenafil Besylate 30 mg IR + 100 mg MR (N=66)	Cialis 20mg (N=66)	Placebo (N=61)
Baseline	14.2 (0.74)	14.8 (0.71)	14.0 (0.81)	13.8 (0.75)	14.1 (0.78)
Visit 4 (Week 4/EOT)	25.4 (1.14)	26.8 (0.98)	27.5 (1.02)	29.3 (0.85)	15.4 (1.03)
Estimated difference vs placebo (95% CI)	10.03 (7.25,12.8)	11.18 (8.43,13.9)	12.17 (9.46,14.9)	13.96 (11.2,16.7)	-
p-value	<0.001	<0.001	<0.001	<0.001	-

CI = confidence interval; EOT = end of treatment; FAS = full analysis set; IR = immediate release; MR = modified release; N = number of subjects; QEQ = quality of erection questionnaire; SE = standard error; vs = versus.

Safety Results: The number of subjects reporting AEs was similar in all active treatment groups although across the gisadenafil besylate treatment groups the numbers of subjects with AEs increased slightly with dose. The overall summary of AEs is presented in Table 11.

Table 11. Overall Summary of Adverse Events

Number of Subjects (%) All Causality	Gisadenafil Besylate 30 mg IR (N=65)	Gisadenafil Besylate 15 mg IR + 50 mg MR (N=67)	Gisadenafil Besylate 30 mg IR + 100 mg MR (N=69)	Cialis 20 mg (N=68)	Placebo (N=66)
No. of AEs	81	74	72	86	31
Subjects with:					
AEs	33 (50.8)	38 (56.7)	40 (58.0)	35 (51.5)	20 (30.3)
SAEs	1 (1.5)	0	0	2 (2.9)	0
Severe AEs	4 (6.2)	3 (4.5)	1 (1.4)	3 (4.4)	2 (3.0)
Discontinuations due to AEs	4 (6.2)	3 (4.5)	3 (4.3)	1 (1.5)	1 (1.5)
Dose reductions/ temporary discontinuations due to AEs	0	0	1 (1.4)	1 (1.5)	1 (1.5)
Treatment Related					
No. of AEs	65	53	63	63	12
Subjects with:					
AEs	27 (41.5)	31 (46.3)	33 (47.8)	27 (39.7)	9 (13.6)
SAEs	1 (1.5)	0	0	0	0
Severe AEs	3 (4.6)	2 (3.0)	1 (1.4)	2 (2.9)	1 (1.5)
Discontinuations due to AEs	3 (4.6)	3 (4.5)	3 (4.3)	0	0
Dose reductions/ temporary discontinuations due to AEs	0	0	1 (1.4)	1 (1.5)	1 (1.5)

AEs = adverse events; IR = immediate release; MR = modified release; N = number of subjects; No. = number; SAEs = serious adverse events.

Incidence of Adverse Events: AE incidence is summarised by frequency in Table 12 for AEs reported by >2 subjects in any treatment group.

The most common all causality and treatment-related AEs after administration of gisadenafil besylate were headache and flushing. Headache was also the most frequently reported AE after Cialis followed by flushing and dyspepsia. The most common all causality and treatment-related AE reported after placebo was headache, although this was only reported by 2 subjects. The majority of AEs were resolved by the end of the study.

Table 12. Incidence of Adverse Events by Frequency (>2 subjects)

All Causality	Gisadenafil Besylate 30 mg IR (N=65)	Gisadenafil Besylate 15 mg IR + 50 mg MR (N=67)	Gisadenafil Besylate 30 mg IR + 100 mg MR (N=69)	Cialis 20 mg (N=68)	Placebo (N=66)
Upper abdominal pain	1 (1.5%)	0	3 (4.3%)	1 (1.5%)	0
Diarrhea	3 (4.6%)	3 (4.5%)	2 (2.9%)	5 (7.4%)	1 (1.5%)
Dyspepsia	1 (1.5%)	2 (3.0%)	6 (8.7%)	4 (5.9%)	0
Influenza	0	0	0	2 (2.9%)	3 (4.5%)
Back pain	1 (1.5%)	0	0	4 (5.9%)	0
Headache	13 (20.0%)	17 (25.4%)	19 (27.5%)	11 (16.2%)	2 (3.0%)
Nasal congestion	6 (9.2%)	3 (4.5%)	3 (4.3%)	2 (2.9%)	1 (1.5%)
Flushing	9 (13.8%)	8 (11.9%)	13 (18.8%)	6 (8.8%)	0
Hot flush	3 (4.6%)	2 (3.0%)	2 (2.9%)	2 (2.9%)	0
Treatment-Related					
Upper abdominal pain	1 (1.5%)	0	3 (4.3%)	1 (1.5%)	0
Diarrhea	2 (3.1%)	3 (4.5%)	2 (2.9%)	4 (5.9%)	0
Dyspepsia	1 (1.5%)	2 (3.0%)	5 (7.2%)	4 (5.9%)	0
Back pain	1 (1.5%)	0	0	4 (5.9%)	0
Headache	13 (20.0%)	15 (22.4%)	18 (26.1%)	11 (16.2%)	2 (3.0%)
Nasal congestion	6 (9.2%)	3 (4.5%)	3 (4.3%)	2 (2.9%)	1 (1.5%)
Flushing	9 (13.8%)	8 (11.9%)	13 (18.8%)	6 (8.8%)	0
Hot flush	3 (4.6%)	1 (1.5%)	2 (2.9%)	2 (2.9%)	0

IR = immediate release; MR = modified release; N = number of subjects.

Serious Adverse Events: Three (3) subjects had SAEs during active treatment. One (1) subject (gisadenafil besylate 30 mg IR) was discontinued from the study and hospitalized after a transient ischaemic attack on Day 13, the subject recovered. The Investigator considered the event to be treatment related but the Sponsor concluded that the event was not treatment related. Another subject (Cialis 20 mg) was hospitalized with acute arthritis in his left shoulder for 10 days from Day 20 caused by a previous fracture. The third subject (Cialis 20 mg) was discontinued from the study and hospitalized with events arising from alcohol abuse from Day 16: alcohol withdrawal symptoms, pancreatitis and a subcomatous episode. His hospitalization was prolonged after he developed severe fever on Day 38 as a consequence of the pancreatitis.

Deaths: There were no deaths during the study.

Permanent Discontinuations due to AEs: There were 12 permanent discontinuations due to treatment-emergent AEs during the study of which 9 were considered treatment related by the Investigator (Table 12).

Table 13. Discontinuation due to Treatment-Related Adverse Events

Serial Number	Event	Duration (days)	Severity	Outcome
Gisadenafil Besylate 30 mg IR				
1	Angina pectoris	6	Severe	Resolved
	Nervousness	6	Moderate	Resolved
2	Transient ischaemic attack[a]	1	Severe	Resolved
3	Headache	8	Moderate	Resolved
	Somnolence	8	Moderate	Resolved
Gisadenafil Besylate 15 mg IR + 50 mg MR				

1	Increased blood glucose	8	Severe	Resolved
2	Abdominal pain	6	Moderate	Resolved
	Diarrhea	6	Mild	Resolved
	Dyspepsia	6	Mild	Resolved
3	Headache	7	Severe	Resolved
Gisadenafil Besylate 30 mg IR + 100 mg MR				
1	Dyspepsia	6	Moderate	Resolved
2	Malaise	1	Severe	Resolved
	Vomiting	1	Severe	Resolved
	Headache	1	Severe	Resolved
3	Hot flushes	4	Moderate	Resolved
	Blurred vision	4	Mild	Resolved
	Headache	3	Mild	Resolved

IR = immediate release; MR = modified release.
a. Reported as a serious adverse event.

Dose Reductions or Temporary Discontinuations due to AEs: Three (3) subjects temporarily discontinued due to AEs during the study. They were all considered treatment related by the Investigator.

Laboratory Evaluations: The median changes from Baseline to last observation did not vary significantly among the treatment groups for all laboratory test parameters and vital signs.

CONCLUSIONS: Gisadenafil Besylate was efficacious at all doses tested. Efficacy was reached at the statistically significant level of 5% for the primary endpoint of the proportion of responders based on successful erections between 12-16 hours postdose for the gisadenafil besylate groups and Cialis when compared with placebo. Similar results were observed for the secondary endpoints: the proportion of good responders based on successful erections and the proportion of responders based on successful intercourses between 12-16 hours postdose, IIEF Question 3 (frequency of penetration), IIEF Question 4 (maintenance of erection), the IIEF EF score, dichotomised GEQs 1 and 2 and the (standardised) overall QEQ score. The responder rates were generally high with an unexpectedly high response to the IR 30 mg dose. Cialis showed the highest responder rate (numerically) in all endpoints except for the "good responder rate". Across the gisadenafil besylate treatment groups, for the endpoints derived from the subject event log, the 30 mg IR group produced the greatest numerical increase from Baseline. For questionnaire derived endpoints the 30 mg IR + 100 mg MR group produced the greatest numerical increase from Baseline.

Gisadenafil Besylate was well tolerated by subjects with erectile dysfunction. The AE profile of gisadenafil besylate was similar to other PDE5 inhibitors. The most common all causality and treatment-related AEs after gisadenafil besylate were headache and flushing. Headache was also the most frequently reported AE after Cialis followed by flushing and dyspepsia. TEAEs were primarily mild or moderate. In total, 12 subjects withdrew from the study due to treatment-emergent AEs. The most common AE leading to discontinuation was headache, reported by 4 of the 10 gisadenafil besylate subjects who discontinued. SAEs were reported by 3 subjects during active treatment although none were considered related to treatment by both the Investigator and Sponsor. Blood in the urine and increases in basophils were the most commonly reported laboratory abnormalities.