Synopsis

Identifier: GM2007/00603/00 **Study Number:** NOS103325

Title: A Multicentre, Two-Part, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Tolerability and Pharmacokinetics of the iNOS Inhibitor GW274150 Administered up to 120 mg Daily for 12 Weeks in the Prophylactic Treatment of Migraine

Investigator(s): Multicentre study.

Study centre(s): Part 1: 18 centres in 6 countries (Belgium [3 centres], Denmark [1], France [3], Germany [3], Netherlands [4] and Norway [4]); Part 2: 48 centres in 8 countries (Denmark [2], Finland [5], France [8], Germany [7], Italy [7], Netherlands [10], Norway [6] and Spain [3]).

Publication(s): None at the time of this report.

Study Period: Part 1: 27 October 2005 to 8 June 2006; Part 2: 12 January 2007 to 15 September 2007.

Phase of Development: II

Objectives:

The primary objective of the study was to estimate the dose-response and dose-safety relationships for GW274150 in the prophylaxis of migraine.

The secondary objectives of the study were:

- to explore efficacy of each dose of GW274150 compared with placebo using various clinical endpoints in the prophylaxis of migraine headaches
- to investigate the safety and tolerability of GW274150 in the prophylaxis of migraine headaches
- to evaluate the pharmacokinetics (PK) of GW274150
- to evaluate the effect of repeat dose treatment of GW274150 upon the generation of nitric oxide (NO) by reference to tyrosine and its nitrosylated derivative-NO tyrosine (Part 2 only)
- to evaluate the relationship between systemic GW274150 exposure and the prophylaxis of migraine headaches
- to evaluate the relationship between systemic GW274150 exposure and safety and tolerability endpoints in migraineurs
- to explore potential relationships between genetic variants and GW274150 efficacy endpoints

- to determine the change in migraine-related quality of life, treatment satisfaction and productivity in subjects treated prophylactically with oral daily GW274150 compared with subjects treated prophylactically with placebo

Methodology:

This was a Phase II, multicentre, randomised (stratified according to number of Baseline migraine headache days ≤8 versus >8), double-blind, placebo-controlled, parallel-group, 2-part study to investigate the efficacy and safety of GW274150 in the prophylaxis of migraine. The maximum duration of this study for any 1 subject in either Part 1 or Part 2 was 20 weeks, consisting of a 4-week Baseline Period (during which no study medication was given), a 12-week double-blind Treatment Period, and a 4-week Follow-Up period. Subjects were not permitted to take part in both Part 1 and Part 2 of the study.

In Part 1, adult male and female subjects with migraine were randomised (1:1:1) to receive GW274150 60 mg, GW274150 120 mg or placebo once daily. It was planned to randomise approximately 120 subjects to achieve 30 subjects per group completing Part 1.

After all subjects randomised into Part 1 of the study either completed the 12-week Treatment Period or discontinued the study, an interim analysis was conducted to determine the course of action for Part 2 of the study. Notwithstanding any safety concerns, after the interim analysis, there were 3 options for Part 2 of the study:

- Option 1: if there was evidence of a strong treatment effect (40% risk reduction versus placebo), then Part 2 would proceed with up to 4 active doses (GW274150 5 to 120 mg once daily) to explore the full dose response curve as well as the dose-safety relationship
- Option 2: if more information was needed on the doses from Part 1, the objective of Part 2 would be to increase the certainty around the observed estimates. The same doses as in Part 1 (GW274150 60 mg and/or 120 mg once daily) and placebo would be studied in Part 2. The sample size would be increased to match the objective.
- Option 3: if there was no evidence of a treatment effect, the study would be terminated

Following the interim analysis, Option 2 was selected and it was decided that Part 2 of the study would evaluate GW274150 60 mg for 12 weeks in an additional group of female subjects.

In Part 2, female subjects were randomised (1:1) to receive either GW274150 60 mg or placebo once daily. It was planned to randomise approximately 320 subjects in order to achieve approximately 240 evaluable subjects completing Part 2.

Number of subjects:

Part 1	Placebo	GW274150 60 mg	GW274150 120 mg
Number of subjects planned, N	40	40	40
Randomised, N	38	37	37
Completed study, n (%)	33 (87)	33 (89)	31 (84)
Total number of subjects withdrawn, n (%)	5 (13)	4 (11)	6 (16)
Withdrawn due to adverse events, n (%)	2 (5)	2 (5)	3 (8)
Withdrawal due to lack of efficacy, n (%)	0	0	0
Withdrawn for other reasons, n (%)	3 (8)	2 (5)	3 (8)
Part 2	Placebo	GW274150 60 mg	
Number of subjects planned, N	160	160	
Randomised, N	154	160	
Completed study, n (%)	135 (88)	142 (89)	
Total number of subjects withdrawn, n (%)	19 (12)	18 (11)	
Withdrawn due to adverse events, n (%)	4 (3)	5 (3)	
Withdrawal due to lack of efficacy, n (%)	1 (<1)	1 (<1)	
Withdrawn for other reasons, n (%)	14 (9)	12 (8)	

Diagnosis and main criteria for inclusion:

Male or female subjects were eligible for Part 1 and female subjects were eligible for Part 2. Females unable to bear children were eligible, and females able to bear children were eligible provided they were not pregnant and using adequate contraception. Subjects were to be aged 18 to 55 years, suffering from migraine with or without aura, according to 2004 International Headache Society criteria 1.1 and 1.2.1, but otherwise healthy. Subjects were to have had migraine for ≥1 year, and be <50 years old at the age of onset. Subjects were to have consistent migraine headache over time (i.e., incidence and severity), have ≥3 migraine headache attacks but <15 headache days (migraine or non-migraine) per month in each of the 3 months prior to the Screening Visit and to maintain this requirement during the Baseline Period. Subjects must have also been able to distinguish migraine headache attacks as discrete attacks from other headaches (i.e., tension-type headaches).

Treatment administration:

Part 1

Subjects were randomised (1:1:1) to receive:

- Placebo (matching GW274150) (4 tablets once daily – 4 placebo tablets)
- GW274150 60 mg (4 tablets once daily – 2 x 30 mg tablets plus 2 placebo tablets)
- GW274150 120 mg (4 tablets once daily – 4 x 30 mg tablets)

The following batch numbers were used: GW274150: 051078996, 051092455; GW274150 placebo: 051078992.

Part 2

Subjects were randomised (1:1) to receive:

- Placebo (matching GW274150) (2 placebo tablets once daily)
- GW274150 60 mg (2 x 30 mg tablets once daily)

The following batch numbers were used: GW274150: 061123914, 061123913; GW274150 placebo: 061118361.

Tablets were taken whole with a glass of water at approximately the same time each morning.

Criteria for evaluation:

The primary efficacy endpoint was the probability of a migraine headache day (MHD) on each day during the 4-week Baseline Period and the 12-week Treatment Period. An MHD was defined as a calendar day with any occurrence of migraine headache pain of ≥30 minutes in duration.

Secondary efficacy endpoints analysed at the end of Part 1 and Part 2 were:

- change from Baseline in the number of MHDs for each 4-week Treatment Period and for the entire Treatment Period
- proportion of subjects with percent reduction from Baseline in number of MHDs (responder rates) of at least 50%, 75%, 90%, and 100% for each 4-week Treatment Period and for the entire Treatment Period
- change from Baseline in the number of migraine attacks for each 4-week Treatment Period and for the entire Treatment Period
- proportion of subjects with percent reduction from Baseline in number of migraine attacks of at least 50%, 75%, 90%, and 100% for each 4-week Treatment Period and for the entire Treatment Period
- change from Baseline in the mean peak migraine pain severity utilising the 4-point pain scale for each 4-week Treatment Period and for the entire Treatment Period
- change from Baseline in mean migraine headache duration for each 4-week Treatment Period and for the entire Treatment Period

Secondary efficacy endpoints analysed at the end of Part 2 only but not including data collected from Part 1 were:

- change from Baseline in the number of migraine headache periods for each 4-week Treatment Period and for the entire Treatment Period
- proportion of subjects with percent reduction from Baseline in number of migraine headache periods of at least 50%, 75%, 90%, and 100% for each 4-week Treatment Period and for the entire Treatment Period

- change from Baseline in percent of migraine attacks with nausea for each 4-week Treatment Period; similar endpoints were analysed for vomiting, photophobia and phonophobia and for the entire Treatment Period
- change from Baseline in percent of migraine attacks with aura for each 4-week Treatment Period and for the entire Treatment Period
- change from Baseline in number of days of acute breakthrough medication administration for each 4-week Treatment Period and for the entire Treatment Period
- change from Baseline (Randomisation Visit) in Migraine Specific Quality of Life Questionnaire Version 2.1 (MSQ v2.1) composite score and subscales (role function-restrictive, role function-preventive, emotional function) at Week 4, 8, 12 and Follow-Up Visits (performed only in those countries with a validated translation of the MSQ v2.1)
- productivity as measured by lost time equivalents (LTE), which is a composite measure of presenteeism (continued to work while under the influence of migraine symptoms) and absenteeism (time missed from work due to migraine). LTE was applied to productivity for work and non-work activities
- treatment satisfaction measured using 3 global items: satisfaction with overall medication effectiveness, satisfaction with side effects, and overall satisfaction at Randomisation, Week 4, 8 and 12 visits (performed only in Part 2 of the study)
- the relationship between GW274150 dose and safety and tolerability
- population PK parameters of GW274150
- change from Baseline in NO-tyrosine, tyrosine and their ratio
- the relationships between systemic GW274150 exposure and the primary and secondary endpoints

Note: Only the following secondary efficacy endpoints are displayed in the synopsis of this Abbreviated Clinical Study: change from Baseline in the number of MHDs; proportion of subjects with percent reduction from Baseline in number of MHDs of at least 50%; change from Baseline in the number of migraine attacks; proportion of subjects with percentage reduction from Baseline in number of attacks of at least 50%; change from Baseline in the mean peak migraine pain severity; and change from Baseline in mean migraine attack duration. In addition, data on PK and pharmacodynamics (PD) variables are presented. Data on additional protocol-specified secondary endpoints are presented in the tables and figures associated with the Abbreviated Clinical Study Report.

The primary safety endpoints were:

- the incidence and severity of clinical adverse events
- changes from Baseline to Weeks 2, 4, 6, 8 and 12 visits in clinical laboratory parameters and vital signs
- electrocardiogram abnormalities at the Weeks 4, 8 and 12 visits.

Pharmacogenetic endpoints included evaluation of the relationship between genetic variants and the PK of GW274150, the relationship between genetic variants and safety and/or tolerability of GW274150 and the relationship between genetic variants and efficacy of GW274150. Pharmacogenetic samples were taken but were not analysed as GW274150 showed no statistically significant efficacy benefits over placebo.

Statistical methods:

The Intent-To-Treat (ITT) Population was defined as all randomised subjects who took at least 1 dose of study medication (as indicated in an Evening Report completed on the electronic diary) and had at least 1 post-Baseline efficacy assessment (i.e., reported a headache event, recorded an entry in the daily log, or completed a health outcomes questionnaire). The ITT Population was used for the primary and secondary efficacy analyses. The Safety Population was defined as all randomised subjects who took at least 1 dose of study medication. The Per-Protocol (PP) Population included subjects in the ITT Population who adhered to major protocol requirements. A modified per-protocol (MPP) Population was defined that included those subjects taking non-allowed medications for ≥10 or ≥15 days per month, since there was concern about a potential bias excluding those subjects who had the most MHDs from the analysis population. The MPP Population was used to analyse the exploratory endpoints in Part 1 and the primary endpoint in Part 2.

In Part 1, for a sample size of 30 per arm, the power (95% confidence interval) of detecting a difference between active treatment and placebo when the true drug effect was 40% is 95% (92 to 97%). Historical data suggest a 25% dropout rate between Randomisation and study completion. Therefore, 40 subjects per treatment arm or a total of 120 subjects were to be randomised to achieve 90 subjects completing Part 1. Part 2 of this study was powered at 80% (n=120/arm) to detect a difference of 25% reduction from placebo in the probability of an MHD on GW274150 60 mg versus placebo.

For Part 1, the null hypothesis of no difference in the log likelihoods for GW274150 60 mg or 120 mg compared with placebo was tested by fitting a logistic hazard model to the observed data using non-linear mixed effect modelling analysis. No adjustment for multiple comparisons was made. Secondary analyses were performed for each active treatment group versus placebo for the change from Baseline in the number of MHDs, number of migraine headache attacks, mean peak migraine pain severity, and mean migraine attack duration for the last 4 weeks of treatment, each 4-week Treatment Period, and the entire 12-week Treatment Period, using a rank analysis of covariance adjusting for Baseline number of events and country. The proportion of subjects with percent reduction from Baseline in the number of MHD of at least 50%, 75%, 90% and 100% was analysed using a conditional logistic regression model adjusting for country if ≥5 responders in each treatment group; otherwise Fisher's exact test without adjustment was used. All tests were 2-sided.

For Part 2, analysis of the primary and secondary endpoints were performed for GW274150 60 mg versus placebo as described for Part 1.

For PK analyses, the GW274150 exposures at steady-state for each subject were estimated via non-linear mixed effect analysis (population PK). The ITT Population was used for these analyses. For PD analyses, summary statistics were presented for NO-tyrosine, tyrosine and the ratio (NO tyrosine:tyrosine) at Baseline (Randomisation Visit), Week 4, 8, and 12. A rank analysis of covariance adjusting for country and the Baseline parameter value was used to compare GW274150 60 mg to placebo at Week 4, 8 and 12. The Safety Population was used for these analyses.

Summary:

Demographics and Baseline characteristics

In Part 1, the majority of subjects were female and the mean age of the study population was approximately 40 years. The majority of subjects were White/Caucasian and were classified as historically having migraine without aura. The subjects had a median number of 4 migraine attacks per month and a median migraine onset age of 16 years.

In Part 2, all subjects were female and had a mean age of approximately 39 years. The majority of subjects were White/Caucasian and were classified as historically having migraine without aura. The subjects had a median number of 4.0 migraine attacks per month and a median migraine onset age of 18 years.

Efficacy results:

Primary efficacy results

In Part 1, for the primary efficacy endpoint of the probability of having an MHD during the last month, no statistically significant treatment advantage was found for either GW274150 60 mg or GW274150 120 mg compared with placebo.

Part 1 was underpowered for the treatment effect size of interest of 25%. Thus, the decision was taken to collect more information with more subjects in Part 2. Exploratory analysis of the Part 1 data suggested a potentially greater response in female subjects at GW274150 60 mg. Therefore, it was decided to study women only in Part 2 at the GW274150 60 mg dose as this would provide the highest chance of observing a treatment effect and focus on the target population.

In Part 2, the Part 1 result was confirmed and no statistically significant treatment advantage was found in the GW274150 60 mg group compared with placebo.

Summary of the Probability of a Migraine Headache Day at Day 70 (ITT Population)

Part 1	Baseline (N=111)	Placebo (N=38)	GW274150 60 mg (N=37)	GW274150 120 mg (N=36)
Probability of a migraine headache day	0.257	0.174	0.144	0.187
95% CI	0.238, 0.277	0.115, 0.254	0.074, 0.260	0.098, 0.325
Treatment group probability change from Baseline (%)	-	32.5	44.1	27.5
95% CI	-	6.1, 58.9	9.3, 79.0	-15.9, 70.9
Risk reduction compared with placebo (%)	-	-	17.2	-7.5
95% CI	-	-	-21.1, 55.6	-57.1, 42.2
Part 2	**Baseline (N=314)**	**Placebo (N=154)**	**GW274150 60 mg (N=160)**	
Probability of a migraine headache day	0.254	0.166	0.190	
95% CI	0.242, 0.265	0.144, 0.191	0.153, 0.232	
Treatment group probability change from Baseline (%)	-	34.5	25.3	
95% CI	-	24.8, 43.2	39.7, 8.5	
Risk reduction compared with placebo (%)	-	-	-14.1	
95% CI	-	-	-32.1, 3.9	

NOTE: Day 70 refers to the last month of the study, i.e., the third 4-week Treatment Period (middle of third treatment month).
CI Confidence interval.

Secondary efficacy endpoints

In Part 1 of the study, there were no statistically significant benefits of treatment with GW274150 60 mg or GW274150 120 mg compared with placebo in any of the key secondary efficacy endpoints.

In Part 2 of the study, there was no statistically significant advantage observed for GW274150 60 mg compared with placebo based on analysis of change from Baseline in the number of MHD. In both treatment groups, there was a reduction from Baseline in the number of migraine headache days, number of migraine attacks, and migraine attack duration. For several of the endpoints, treatment with placebo demonstrated an advantage over treatment with GW274150 60 mg.

The key secondary efficacy endpoints for Part 2 are presented in the table below.

Part 2 Key Secondary Efficacy Endpoints (ITT Population)

Part 2	Placebo (N=154)	GW274150 60 mg (N=160)
Number of Migraine Headache Days - Change from Baseline in the Last 4-Week Treatment Period		
n	150	155
Median (range)	-2.94 (-17.0 to 10.0)	-2.38 (-15.1 to 9.8)
95% CI	-3.781, -2.500	-2.801, -1.654
p-value	-	0.016
Subjects with 50% Reduction from Baseline in Migraine Headache Days - Last 4-Week Treatment Period		
Subjects with 50% reduction, n (%)	71 (47)	64 (41)
Odds ratio	-	0.771
95% CI	-	0.479, 1.239
p-value	-	0.282
Number of Migraine Attacks - Change from Baseline in the Last 4-Week Treatment Period		
n	150	155
Median (range)	-1.96 (-8.0 to 4.2)	-1.37 (-8.2 to 3.3)
95% CI	-2.166, -1.537	-1.742 to -1.106
p-value	-	0.008
Subjects with 50% Reduction from Baseline in Migraine Attacks - Last 4-Week Treatment Period		
Subjects with 50% reduction, n (%)	80 (53)	60 (39)
Odds ratio	-	0.528
95% CI	-	0.329, 0.850
p-value	-	0.009
Mean Peak Migraine Pain Severity - Change from Baseline in the Last 4-Week Treatment Period		
n	117	135
Median (range)	0.00 (-1.6 to 1.3)	0.00 (-1.7 to 1.4)
p-value	-	0.768
Mean Migraine Attack Duration - Change from Baseline in the Last 4-Week Treatment Period		
n	117	135
Median (range), hours	-4.83 (-146.3 to 113.7)	-7.23 (-108.8 to 151.4)
95% CI	-11.090, 1.205	-11.000, -0.639
p-value	-	0.619

Safety

In Part 1, adverse events (AEs) were reported in 14 (37%), 17 (46%) and 25 (68%) subjects in the placebo, GW274150 60 mg and GW274150 120 mg groups, respectively. Overall, the most commonly reported AEs were nasopharyngitis, fatigue and influenza in all groups. In Part 2, AEs were reported in 81 (53%) subjects in the placebo group and 89 (56%) subjects in the GW274150 60 mg group. Overall, the most commonly reported AEs were nasopharyngitis and nausea in both treatment groups.

Number (%) of Subjects with Common Adverse Events (5% or More in Any Treatment Group) by Preferred Term During the Treatment Period (Safety Population)

Part 1	Number (%) of subjects		
	Placebo (N=38)	GW274150 60 mg (N=37)	GW274150 120 mg (N=37)
Any AE	14 (37)	17 (46)	25 (68)
Nasopharyngitis	4 (11)	8 (22)	4 (11)
Fatigue	1 (3)	2 (5)	3 (8)
Influenza	1 (3)	1 (3)	3 (8)
Back pain	0	1 (3)	2 (5)
Dizziness	0	1 (3)	2 (5)
Oedema peripheral	0	1 (3)	2 (5)
Flatulence	0	0	2 (5)
Gastroenteritis viral	0	0	2 (5)
Myalgia	0	0	2 (5)
Pharyngolaryngeal pain	0	3 (8)	1 (3)
Insomnia	1 (3)	2 (5)	0
Nausea	2 (5)	0	0
Part 2	Placebo (N=154)	GW274150 60 mg (N=160)	
Any AE	81 (53)	89 (56)	
Nasopharyngitis	9 (6)	12 (8)	
Nausea	8 (5)	9 (6)	
Back pain	4 (3)	8 (5)	
Fatigue	7 (5)	3 (2)	
Cystitis	7 (5)	1 (<1)	

Note: A subject may have had more than 1 incidence of each adverse event.

In Part 1, 1 subject (GW274150 60 mg group) had a serious adverse event (SAE) of moderate tremor. The event was considered by the investigator to be related to the study drug and investigational product was withdrawn. In Part 2, there were 5 subjects with SAEs (2 and 3 subjects in the placebo and GW274150 60 mg groups, respectively) and no SAEs were considered to be related to study treatment.

Number (%) of Subjects with Serious Adverse Events by Preferred Term During the Treatment Period (Safety Population)

Part 1	Number (%) of subjects		
	Placebo (N=38)	GW274150 60 mg (N=37)	GW274150 120 mg (N=37)
Any SAE	0	1 (3)	0
Tremor	0	1 (3)	0
Part 2	Placebo (N=154)	GW274150 60 mg (N=160)	
Any AE	2 (1)	3 (2)	
Pelvic fracture	0	1 (<1)	
Sternal fracture	0	1 (<1)	
Tendon rupture	0	1 (<1)	
Coronary artery occlusion	1 (<1)	0	
Appendicitis	1 (<1)	0	
Musculoskeletal chest pain	0	1 (<1)	
Pneumothorax	0	1 (<1)	

Note: A subject may have had more than 1 incidence of each adverse event.

In Part 1, a similar percentage of subjects had AEs leading to withdrawal from the study in each treatment group. Only peripheral oedema was reported in more than 1 subject (2 subjects in the GW274150 120 mg group). In Part 2, a similar percentage of subjects had AEs leading to withdrawal from the study in each treatment group. No AE leading to withdrawal was reported in more than 1 subject.

Number (%) of Subjects with Adverse Events Leading to Permanent Discontinuation of Investigational Product (by Preferred Term) (Safety Population)

Part 1	Number (%) of subjects		
	Placebo (N=38)	GW274150 60 mg (N=37)	GW274150 120 mg (N=37)
Any AE	2 (5)	2 (5)	3 (8)
Oedema peripheral	0	0	2 (5)
Blood creatine kinase increased	0	0	1 (3)
Constipation	0	0	1 (3)
Drug hypersensitivity	0	0	1 (3)
Face oedema	0	0	1 (3)
Hepatic enzyme increased	0	0	1 (3)
Weight increased	0	0	1 (3)
Dizziness	0	1 (3)	0
Fatigue	0	1 (3)	0
Syncope	0	1 (3)	0
Tremor	0	1 (3)	0
Balance disorder	1 (3)	0	0
Nausea	1 (3)	0	0
Palpitations	1 (3)	0	0
Tension headache	1 (3)	0	0
Part 2	Placebo (N=154)	GW274150 60 mg (N=160)	
Any AE	4 (3)	5 (3)	
Gastroenteritis	0	1 (<1)	
Headache	0	1 (<1)	
Memory impairment	0	1 (<1)	
Pelvic fracture	0	1 (<1)	
Pneumothorax	0	1 (<1)	
Sternal fracture	0	1 (<1)	
Urticaria	0	1 (<1)	
Abdominal distension	1 (<1)	0	
Abdominal pain upper	1 (<1)	0	
Acne	1 (<1)	0	
Asthenia	1 (<1)	0	
Coronary artery occlusion	1 (<1)	0	
Fatigue	1 (<1)	0	
Oedema peripheral	1 (<1)	0	

Note: A subject may have had more than 1 incidence of each adverse event.

There was no evidence of a consistent drug effect on laboratory, electrocardiogram or vital sign parameters during either part of the study.

Pharmacokinetic endpoints

The plasma concentrations observed in this study corresponded well with the predictions of the population PK model, which was based on the Phase I data, and PK parameters could be estimated for all individuals included in the analysis. Steady state plasma exposures of GW274150 were as expected in the majority of subjects.

Pharmacodynamic endpoints

There was a slight trend in both treatment groups for the NO-tyrosine and tyrosine values to increase as the study progressed. However, there was no statistically significant difference between the placebo and GW274150 60 mg groups in change from Baseline in NO-tyrosine, tyrosine or NO-tyrosine:tyrosine ratio at Week 4, Week 8 or Week 12.

Conclusions:

- GW274150 60 mg showed no statistically significant efficacy benefits over placebo for the primary or secondary efficacy endpoints. Hence, no dose-response relationship could be established.
- Doses of GW274150 60 mg and 120 mg were generally well-tolerated. No safety signals were identified. The data did not suggest that treatment with GW274150 60 mg or GW274150 120 mg was associated with any significant safety risk compared with placebo. No dose-safety relationship was established since no major safety signals were observed, and no full dose-response relationship was investigated in this study.
- Steady state plasma exposures of GW274150 were as expected in the majority of subjects.
- There was no statistically significant difference between the placebo and GW274150 60 mg groups in change from Baseline in NO-tyrosine, tyrosine or NO-tyrosine:tyrosine ratio.
- The results of this study do not support the use of GW274150 60 mg for the prophylactic treatment of migraine in adult male or female subjects suffering from migraine with or without aura.

Date of Report: April 2008