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: KIP112967

Title: A randomised, double blind study to evaluate the safety and efficacy of the p38 kinase inhibitor, GW856553, in subjects with neuropathic pain from peripheral nerve injury

Rationale: GW856553, a potent adenosine triphosphate binding site inhibitor of p38α mitogen-activated protein kinase, has previously been shown to have a statistically significant effect in a validated preclinical model of neuropathic pain. This study was designed to evaluate the efficacy of oral dosing with GW856553 7.5 mg twice daily or placebo for 28 days in subjects with neuropathic pain resulting from peripheral nerve injury due to either trauma or surgery.

Phase: IIa

Study Period: 31 August 2009 to 19 July 2010

Study Design: Randomised, double-blind, placebo-controlled, parallel group

Centres: 20 centres in 7 countries (Australia: 1, Denmark: 3, Norway: 4, Russian Federation: 3, Spain: 5, Sweden: 3, United Kingdom: 1)

Indication: Neuropathic pain

Treatment: Oral dosing with GW856553 7.5 mg twice daily (BID) or placebo for 4 weeks (28 days).

Objectives: The primary objective was to investigate the effect of repeat oral dosing (28 days) of GW856553 on neuropathic pain in subjects with peripheral nerve injury.

Primary Outcome/Efficacy Variable:

Change in average daily pain score from baseline to Week 4 of treatment based on the 11-point pain intensity numeric rating scale (PI-NRS) (0=no pain, 10=maximum pain imaginable). *Subjects were to specifically rate the pain intensity for the neuropathic pain associated with the nerve injury and not pain from other concomitant causes.*

Secondary Outcome/Efficacy Variable(s):

- Change in average daily pain score from baseline to Weeks 1, 2 and 3 of treatment and the week before the follow-up visit.
- Change in intensity of dynamic allodynia (rating scale of 0 to 10, with 0=no pain, 10=maximum pain) from baseline to Days 14 and 28 of treatment.
- Change in intensity of static hyperalgesia (rating scale of 0 to 10, with 0=no pain, 10=maximum pain) from baseline to Days 14 and 28 of treatment.
- Change in pain quality on the Short-Form McGill Pain Questionnaire (SF-MPQ) from baseline to Days 14 and 28 of treatment and the follow-up visit.
- Change in Galer Neuropathic Pain Scale (NPS) from baseline to Days 14 and 28 of treatment and the follow-up visit.
- Proportion of subjects who have ≥30% and ≥50% reduction in average daily pain score relative to baseline during Weeks 1, 2, 3 and 4 of treatment and the week before follow-up.
- Proportion of subjects who have “improved”, “much improved” or “very much improved” relative to baseline on the Patient’s Global Impression of Change (PGIC) on Days 14 and 28 of treatment and the follow-up visit.
- Proportion of subjects who have “improved”, “much improved” or “very much improved” relative to baseline on the Clinical Global Impression of Change (CGIC) on Days 14 and 28 of treatment and the follow-up visit.
- Change in the amount of rescue medication used from baseline to Week 4 of treatment.
- Change in total Profile of Mood States (POMS) score and POMS domains scores from baseline to Weeks 2 and 4 of treatment.
- Change in Sleep Interference Scale (SIS) from baseline to Weeks 1, 2, 3 and 4 of treatment.
- Change in SF-36 Health Survey domains/components from baseline to Day 28 of treatment.
- Pre-dose and post-dose plasma GW856553 concentrations on Days 14 and 28 to assess patient compliance.

Statistical Methods:

Based on a between subject standard deviation of 2.1 for change from baseline in average daily pain scores at Week 4, a sample size of 71 evaluable subjects per arm was required to give 80% power, using a two-sided type I error rate of 5%, and to detect a treatment difference of 1 unit on the 11-point pain intensity numeric rating scale (PI-NRS). Allowing for a 10% withdrawal rate, a total of 79 subjects were required for each treatment arm (158 in total).

The intent-to-treat (ITT) population was used for efficacy analyses. The ITT consisted of all randomised subjects who received at least the first dose of study medication and had at least one post-treatment efficacy assessment.

Continuous endpoints, except SF-36, were analysed by treatment week using a mixed model repeated measures technique. The terms fitted included treatment, treatment*week, baseline, baseline*week, country and therapy group. The point estimate and corresponding 95% confidence interval (CI) were constructed for the treatment difference between GW856553 and placebo groups for each week, with the primary inference being the change at Week 4. SF-36 component/domain scores, and the follow-up time point of other measures were analysed using analysis of covariance adjusting for baseline score, country, and therapy group. The point estimate and corresponding 95% CI were constructed for the treatment difference between GW856553 and placebo groups at Week 4. Binary endpoints were analysed using a generalised estimating equations model. The model included treatment, treatment*week, baseline, baseline*week, country and therapy group if appropriate. The follow-up time point for binary endpoints was analysed using a logistic regression model which included baseline, treatment, country and therapy group if appropriate. The odds ratio for each treatment comparison of interest along with the corresponding 95% CI and p-value were presented. If the endpoint was not formally analysed, then unadjusted (raw) means were presented.

Study Population:

Male or female subjects aged 18-80 years inclusive, with a diagnosis of peripheral neuropathic pain with the following characteristics: focal neuropathic pain related to nerve injury caused by trauma or surgery not associated with an acute medical condition or injury by avulsion; location of pain consistent with the area innervated by the affected nerve(s), with or without other sensory symptoms in the affected area; duration of pain at least 12 weeks since the initial insult.

Subjects who were already taking medications for the treatment of their neuropathic pain (adjunct therapy) were allowed to continue this medication provided they had been on a stable dose and dosing regimen for at least 4 weeks before the baseline period and providing the medication was not otherwise prohibited. Subjects who were not taking any specific treatment for neuropathic pain could also be enrolled (monotherapy).

Non-steroidal anti-inflammatory drugs, cycloxygenase-2 inhibitors and topical lidocaine had to be stopped at least 5 half-lives prior to the start of the baseline period; topical capsaicin had to be stopped at least 8 weeks prior to the start of the baseline period; and the most recent nerve blocks or steroid injections for the treatment of neuropathic pain had to have been administered at least 4 weeks prior to the start of the baseline period. These medications were prohibited during the study.

After wash-out of prohibited medications during a screening period lasting up to approximately 3 weeks, subjects underwent a baseline period of 1 week to determine their baseline average daily pain intensity. Subjects with pain of at least moderate intensity (an average daily pain score of ≥4 on the 11-point PI-NRS at baseline) were eligible for the study, as long as they had recorded an average daily pain score on a minimum of 4 out of the 7 days prior to dosing.

Number of Subjects:	**GW856553**	**Placebo**
Planned, N	79	79
Dosed, N	87	81
Completed, n (%)	78 (90)	73 (90)
Total number subjects withdrawn, n (%)	9 (10)	8 (10)
Withdrawn due to adverse events, n (%)	5 (6)	3 (4)
Withdrawn due to lack of efficacy, n (%)	0	1 (1)
Withdrawn for other reasons, n (%)	4 (5)	4 (5)
Demographics	**GW856553**	**Placebo**
N (ITT)	87	81
Females: Males	56: 31	49:32
Mean age in years (sd)	52.3 (14.11)	51.1 (12.97)
Mean weight in kg (sd)	80.38 (18.099)	77.20 (15.414)
White, n (%)	87 (100)	80 (99)
Asian, n (%)	0	1 (1)

Primary Efficacy Results:

Adjusted mean change from baseline in average daily PI-NRS score

	GW856553 N=87	**Placebo N=81**	**Adjusted mean difference**	**95% CI**	**P-value [a]**
Week 1	-0.49	-0.32	-0.17	-0.50, 0.16	0.3062
Week 2	-0.87	-0.58	-0.29	-0.70, 0.11	0.1569
Week 3	-0.92	-0.79	-0.13	-0.60, 0.35	0.5973
Week 4 *(primary time point)*	-1.04	-0.81	-0.22	-0.73, 0.28	0.3846
Follow-up	-0.90	-0.64	-0.26	-0.72, 0.19	0.2569

Secondary Efficacy Results:					
Adjusted mean change from baseline for secondary efficacy variables					
	GW856553 N=87	**Placebo N=81**	**Adjusted mean difference**	**95% CI**	**P-value [a]**
Intensity of dynamic allodynia					
Week 2	-0.12	-0.12	-0.00	-0.39, 0.38	0.9897
Week 4	-0.09	-0.11	0.02	-0.44, 0.49	0.9301
Intensity of static hyperalgesia					
Week 2	0.04	-0.09	0.13	-0.35, 0.61	0.5926
Week 4	-0.09	-0.11	0.02	-0.48, 0.53	0.9299
Galer NPS Total Score					
Week 2	-7.55	-8.96	1.41	-3.35, 6.18	0.5586
Week 4	-9.58	-11.37	1.79	-3.16, 6.74	0.4770
POMS					
Week 2	-3.84	-6.59	2.76	-4.01, 9.52	0.4218
Week 4	-12.82	-7.91	-4.91	-12.93, 3.11	0.2284
Sleep Interference Scale					
Week 1	-0.52	-0.31	-0.21	-0.52, 0.11	0.1978
Week 2	-0.65	-0.48	-0.18	-0.55, 0.19	0.3481
Week 3	-0.69	-0.81	0.12	-0.35, 0.59	0.6116
Week 4	-0.79	-0.67	-0.12	-0.63, 0.39	0.6463
SF-36 Physical Component					
Week 4	2.11	2.50	-0.40	-2.28, 1.49	0.6793
SF-36 Mental Component					
Week 4	1.16	0.81	0.35	-2.36, 3.06	0.7969
SF-36 Physical Functioning					
Week 4	0.94	2.93	-1.99	-6.96, 2.98	0.4298
SF-36 Bodily Pain					
Week 4	12.73	10.62	2.11	-3.85, 8.07	0.4857
SF-36 General Health					
Week 4	1.29	3.44	-2.14	-6.45, 2.16	0.3265
SF-36 Mental Health					
Week 4	3.13	3.40	-0.27	-5.36, 4.82	0.9164
SF-36 Role Emotional					
Week 4	4.13	3.54	0.59	-7.89, 9.07	0.8910
SF-36 Role Physical					
Week 4	6.28	8.80	-2.52	-10.29, 5.25	0.5223
SF-36 Social Functioning					
Week 4	5.97	1.52	4.45	-2.49, 11.39	0.2070
SF-36 Vitality					
Week 4	-0.38	2.23	-2.61	-8.31, 3.10	0.3679
SF-MPQ Total Score [b]					
Week 2	-3.3	-3.0	ND	ND	ND
Week 4	-3.8	-3.3	ND	ND	ND
Follow-up	-3.0	-2.7	ND	ND	ND
SF-MPQ Affective Score [b]					
Week 2	-1.0	-0.6	ND	ND	ND
Week 4	-1.2	-0.7	ND	ND	ND
Follow-up	-0.9	-0.7	ND	ND	ND
SF-MPQ Sensory Score [b]					
Week 2	-2.4	-2.4	ND	ND	ND
Week 4	-2.7	-2.5	ND	ND	ND
Follow-up	-2.2	-2.0	ND	ND	ND

Proportion of responders					
	GW856553 N=87	**Placebo N=81**	**Adjusted odds ratio**	**95% CI**	**P-value [a]**
≥30% reduction in PI-NRS					
Week 1	7/87 (8%)	5/80 (6%)	1.11	0.34, 3.58	0.8606
Week 2	12/84 (14%)	12/78 (15%)	0.76	0.30, 1.94	0.5677
Week 3	25/82 (30%)	15/74 (20%)	1.62	0.76, 3.45	0.2157
Week 4	25/74 (34%)	21/70 (30%)	1.16	0.58, 2.31	0.6682
Follow-up	19/69 (28%)	15/66 (23%)	1.22	0.51, 2.92	0.6557
≥50% reduction in PI-NRS					
Week 1	2/87 (2%)	2/80 (3%)	0.87	0.11, 6.77	0.8955
Week 2	3/84 (4%)	5/78 (6%)	0.51	0.11, 2.33	0.3828
Week 3	5/82 (6%)	5/74 (7%)	0.90	0.24, 3.32	0.8723
Week 4	8/74 (11%)	7/70 (10%)	0.94	0.33, 2.68	0.9061
Follow-up	6/69 (9%)	4/66 (6%)	1.36	0.36, 5.12	0.6537
PGIC responders [c]					
Week 2	30/82 (37%)	33/79 (42%)	ND	ND	ND
Week 4	37/80 (46%)	31/74 (42%)	ND	ND	ND
Follow-up	36/84 (43%)	28/78 (36%)	ND	ND	ND
CGIC responders [c]					
Week 2	34/82 (41%)	33/78 (42%)	ND	ND	ND
Week 4	39/80 (49%)	34/74 (46%)	ND	ND	ND
Follow-up	43/85 (51%)	28/79 (35%)	ND	ND	ND

a. P-values were not adjusted for multiple comparisons.
b. Unadjusted mean change from baseline shown for SF-MPQ endpoints.
c. Responders defined as “minimally improved”, “much improved” or “very much improved" relative to baseline.
CGIC, Clinical Global Impression of Change; ND, not done; NPS, neuropathic pain scale; PGIC, Patient’s Global Impression of Change; PI-NRS, pain intensity numeric rating scale; SF-MPQ, POMS, Profile of Mood States; SF-MPQ, Short-form McGill Pain Questionnaire.

Pharmacokinetic Results:
319 plasma GW856553 concentration records were collected from 84 subjects, of which 3 were non-quantifiable and 1 was not reportable. Compliance based on the degree of non-quantifiable concentrations indicated that compliance within the study was very high. There was no evidence of a greater reduction in PI-NRS scores with higher GW856553 plasma concentrations.

Safety Results:
Adverse events (AEs) and serious adverse events (SAEs) were collected from the start of Investigational product until follow-up. Any SAEs related to study participation were collected between the time a subject consented to participate in the study up to and including follow-up.

	GW856553 N=87	**Placebo N=81**
Number of subjects with AEs, n (%)	66 (76)	56 (69)
Most Frequent AEs (≥5% in any group):		
Headache	30 (34)	26 (32)
Nausea	12 (14)	6 (7)
Dizziness	6 (7)	5 (6)
Pain in extremity	6 (7)	5 (6)
Arthralgia	5 (6)	2 (2)
Neck pain	4 (5)	3 (4)
Paraesthesia	4 (5)	2 (2)
Back pain	4 (5)	1 (1)
Constipation	4 (5)	0 (0)
Diarrhoea	3 (3)	7 (9)
Nasopharyngitis	3 (3)	5 (6)
Fatigue	2 (2)	4 (5)

Serious Adverse Events, n (%) [n(%) considered by the investigator to be related, possibly related, or probably related to study medication]		
Pneumonia	1 (1) [1 (1)]	0 (0) [0 (0)]

The adjusted mean change from baseline in PI-NRS score at Week 4 of the double-blind treatment period (primary endpoint) was -1.04 and -0.81 units in GW856553 and placebo groups, respectively, and the adjusted mean treatment difference of -0.22 was not statistically significant. Adverse events were reported by 66 (76%) subjects in the GW856553 group and 56 (69%) subjects in the placebo group. The most frequently reported adverse events were headache and nausea in the GW856553 group and headache and diarrhoea in the placebo group. One non-fatal serious adverse event, pneumonia, was reported in the GW856553 group. No serious adverse events were reported in the placebo group. Overall 3 of 84 subjects had non-quantifiable GW856553 plasma concentrations, indicating that compliance within the study was very high. There was no evidence of a greater reduction in PI-NRS scores with higher GW856553 plasma concentrations.