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: KIP113049

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

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 lumbosacral radiculopathy (LSR) with neuropathic pain.

Phase: IIa

Study Period: 07 January 2010 to 23 August 2010

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

Centres: 16 centres in 5 countries (Denmark: 2, France: 5, Germany: 5, Norway: 2, Sweden: 2)

Indication: Neuropathic pain

Treatment: Oral dosing with GW856553 7.5 mg twice daily (BID) or placebo. On Days 1-7 all subjects received placebo (blinded placebo run-in). Randomised double-blind treatment (GW856553 or placebo) was then administered for 4 weeks (28 days), from Day 8-35.

Study weeks are referenced in relation to double-blind treatment, as follows:

- Placebo run-in =(Day 1-7/day before first double-blind dose)/Study Week 1.
- Week 1 = (Day 8 (or first day of double-blind dose) to Day 14)Study Week 2.
- Week 2 = (Day 15 to Day 21)/Study Week 3.
- Week 3 = (Day 22 to Day 28)/Study Week 4.
- Week 4 = (Day 29 to Day 35)/Study Week 5.
- Follow-up = (first 7 days without double-blind dosing, e.g., Day 36 to Day 42)/Follow-up Visit.

Objectives: The primary objective was to investigate the effects of repeat oral dosing of GW856553 on neuropathic pain in subjects with LSR.

Primary Outcome/Efficacy Variable:

- Change in average daily neuropathic pain score from baseline to Week 5 of treatment (Week 4 of double-blind treatment) based on the 11-point PI-NRS (0=no pain, 10=maximum pain imaginable). *Subjects were to specifically rate the pain intensity for the neuropathic pain associated with LSR and not pain from other concomitant causes i.e. subjects rated their pain that related to the symptomatic nerve root(s) perceived in the lower limb and not any concomitant low back pain (if any existed). If the neuropathic pain was perceived in both lower limbs then subjects were to rate the pain in their worst lower limb (their worst limb was determined by history of the intensity of pain at screening and remained the same throughout the study) as the primary endpoint.*

Secondary Outcome/Efficacy Variable(s):

Neuropathic pain from LSR

- Change in average daily pain score from baseline to Weeks 1, 2 and 3 of double-blind treatment and the week before the follow-up visit.
- Change in pain quality on the Short-Form McGill Pain Questionnaire (SF-MPQ) from baseline to Weeks 2 and 4 of double-blind treatment and the follow-up visit.
- Change in Galer Neuropathic Pain Scale from baseline to Weeks 2 and 4 of double-blind treatment and the follow-up visit.
- Proportion of patients who had ≥30% and ≥50% reduction in average daily pain score relative to baseline during Weeks 1, 2, 3 and 4 of double-blind treatment and the week before follow-up.
- Proportion of patients who had “improved”, “much improved” or “very much improved” relative to baseline on the Patient Global Impression of Change (PGIC) at the end of placebo run-in and Weeks 2 and 4 of double-blind treatment and the follow-up visit.
- Proportion of patients who had “improved”, “much improved” or “very much improved” relative to baseline on the Clinical Global Impression of Change (CGIC) at the end of placebo run-in and Weeks 2 and 4 of double-blind treatment and the follow-up visit.

Low back pain in the lumbosacral spine

- Change in average daily pain score from baseline to Weeks 1, 2, 3 and 4 of double-blind treatment and the week

before the follow-up visit.

- Change in pain quality on the SF-MPQ from baseline to Weeks 2 and 4 of double-blind treatment and the follow-up visit.
- Proportion of patients who had ≥30% and ≥50% reduction in average daily pain score relative to baseline during Weeks 1, 2, 3 and 4 of double-blind treatment and the week before follow-up.
- Proportion of patients who had "improved", "much improved" or "very much improved" relative to baseline on the PGIC at the end of placebo run-in and Weeks 2 and 4 of double-blind treatment and the follow-up visit.
- Proportion of patients who had "improved", "much improved" or "very much improved" relative to baseline on the CGIC at the end of placebo run-in and Weeks 2 and 4 of double-blind treatment and the follow-up visit.
- Change in the score of the Oswestry Disability Index from baseline to Week 4 of double-blind treatment.

Other efficacy variables

- Change in the amount of rescue medication used (in terms of dosage/day) from baseline to Week 4 of double-blind treatment.
- Change in total Profile of Mood States (POMS) score and POMS domains scores from baseline to Weeks 2 and 4 of double-blind treatment.
- Change in Sleep Interference Scale from baseline to Weeks 1, 2, 3 and 4 of double-blind treatment.
- Change in SF-36 Health Survey domains/components from baseline to Week 4 of double-blind treatment.
- Change in time to complete timed walk (20 m) from baseline to Week 4 of double-blind treatment.
- Change in walking-associated pain during timed walk from baseline to Week 4 of double-blind treatment.

Pharmacokinetics

- Pre-dose and post-dose plasma GW856553 concentrations on Days 21 and 35 of treatment (Weeks 2 and 4 of double-blind treatment) to assess patient compliance.

Statistical Methods:

Based on a between subject standard deviation of 2.0 for change from baseline to Week 4 of the double-blind period of dosing, a sample size of 64 evaluable subjects per arm was required to detect a between treatment difference of 1 unit on the 11-point pain intensity numeric rating scale (PI-NRS) to ensure 80% power, using a two-sided type I error rate of 5%. Allowing for a 10% withdrawal rate, a total of 142 randomised subjects were required (71 subjects for each treatment arm).

The intent-to-treat (ITT) population was used for efficacy analyses. The ITT consisted of all randomised subjects who received at least one dose of double-blind study medication (after placebo run-in) and had at least one efficacy assessment on double-blind treatment.

Continuous endpoints that were assessed over multiple treatment weeks were analysed using a mixed model repeated measures technique. The terms fitted included treatment, week, treatment*week, baseline score, baseline*week, placebo run-in score , placebo run-in*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. Continuous measures that were assessed only once post-baseline (e.g. SF-36) and the follow-up time point of other measures were analysed using analysis of covariance adjusting for baseline score, placebo-run-in score [if appropriate], country, and therapy group. Binary endpoints were analysed using a generalised estimating equations model. The model included treatment, week, treatment*week, baseline score, baseline*week, placebo run-in score , placebo-run*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 score, placebo run-in score, 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. P-values were not adjusted for multiple comparisons. 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 neuropathic pain due to LSR with the following characteristics: pain perceived in one or both lower limbs at sites consistent with the area innervated by the L4, L5 or S1 nerve roots, with or without other sensory symptoms in the affected areas (typically, the pain may have been perceived in the buttock, thigh, calf, leg, foot or toes); history of the pain suggested that the cause of LSR was due to injury of the lumbosacral nerve root(s) by degenerative disease of the vertebrae in the lumbosacral spine or associated soft tissues including the intervertebral discs, or secondary to spinal injury and not due to infection/abscess, haematoma or malignancy; duration of pain at least 12 weeks since onset; intensity of pain stable for the 2 weeks prior to screening, based on clinical history.

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 randomisation 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 or 2 weeks prior to the start of the baseline period (Day -7), whichever was longer. 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 in which they recorded their average daily pain intensity using the 11-point PI-NRS. Subjects with at least moderate intensity of pain (a mean average daily pain score of ≥4 in their worst lower limb for the baseline week) were eligible to continue into the treatment period, as long as they had recorded an average daily pain score on a minimum of 4 out of the 7 days.

Number of Subjects:	**GW856553**	**Placebo**
Planned, N	71	71
Dosed (received at least one dose during placebo run-in), N	69	75
ITT, N	68	71
Completed, n (%)	63 (93)	68 (96)
Total number subjects withdrawn, n (%)	5 (7)	3 (4)
Withdrawn due to adverse events, n (%)	1 (1)	0
Withdrawn due to lack of efficacy, n (%)	2 (3)	3 (4)
Withdrawn for other reasons, n (%)	2 (3)	0
Demographics	**GW856553**	**Placebo**
N (ITT)	68	71
Females: Males	42:26	34:37
Mean Age in Years (sd)	58.6 (11.02)	58.4 (10.93)
Mean Weight in Kg (sd)	82.94 (15.130)	84.83 (16.156)
White n (%)	68 (100)	71 (100)

Primary Efficacy Results:

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

Time point	**GW856553 N=68**	**Placebo N=71**	**Adjusted mean difference**	**95% CI**	**P-value [a]**
Week 1	-1.08	-0.91	-0.17	-0.49, 0.15	0.2914
Week 2	-1.47	-1.08	-0.39	-0.79, 0.01	0.0581
Week 3	-1.73	-1.25	-0.47	-0.92, -0.03	0.0376
Week 4 *(primary time point)*	-1.91	-1.55	-0.36	-0.84, 0.13	0.1491
Follow-up	-1.55	-1.35	-0.19	-0.75, 0.36	0.4886

Secondary Efficacy Results:

Mean change from baseline for secondary efficacy variables for neuropathic pain

Variable Time point	**GW856553 N=68**	**Placebo N=71**	**Mean difference**	**95% CI**	**P-value [a]**
SF-MPQ Total Score [b]					
Week 2	-4.7	-2.2	ND	ND	ND
Week 4	-5.8	-3.9	ND	ND	ND
Follow-up	-4.4	-3.2	ND	ND	ND
SF-MPQ Affective Score [b]					
Week 2	-1.5	-0.8	ND	ND	ND
Week 4	-2.0	-1.0	ND	ND	ND
Follow-up	-1.5	-0.8	ND	ND	ND
SF-MPQ Sensory Score [b]					
Week 2	-3.2	-1.4	ND	ND	ND
Week 4	-3.8	-2.9	ND	ND	ND
Follow-up	-2.9	-2.4	ND	ND	ND

Galer NPS total score [b]					
Week 2	-10.10	-2.76	-7.34	-12.25, -2.43	0.0037
Week 4	-14.62	-10.11	-4.51	-9.97, 0.95	0.1049
Galer NPS non-allodynic pain score [c]					
Week 2	-11.0	-4.6	ND	ND	ND
Week 4	-15.7	-12.3	ND	ND	ND
Proportion of responders for neuropathic pain					
Variable **Time point**	**GW856553** **N=68**	**Placebo** **N=71**	**Adjusted odds ratio**	**95% CI**	**P-value [a]**
≥30% reduction in PI-NRS					
Week 1	12/67 (18%)	15/71 (21%)	0.79	0.25, 2.48	0.6813
Week 2	29/68 (43%)	18/69 (26%)	3.16	1.26, 7.95	0.0145
Week 3	29/65 (45%)	21/69 (30%)	2.74	1.16, 6.45	0.0213
Week 4	28/65 (43%)	28/68 (41%)	1.23	0.55, 2.72	0.6110
Follow-up	24/57 (42%)	20/55 (36%)	1.47	0.60, 3.56	0.3967
≥50% reduction in PI-NRS					
Week 1	8/67 (12%)	6/71 (8%)	1.92	0.44, 8.46	0.3861
Week 2	11/68 (16%)	7/69 (10%)	3.04	0.75, 12.41	0.1208
Week 3	14/65 (22%)	11/69 (16%)	1.96	0.68, 5.60	0.2114
Week 4	19/65 (29%)	12/68 (18%)	2.82	0.97, 8.20	0.0563
Follow-up	15/57 (26%)	12/55 (22%)	1.33	0.49, 3.61	0.5786
PGIC responders [d]					
Placebo run-in	22/66 (33%)	19/71 (27%)	1.54	0.72, 3.30	0.2687
Week 2	34/67 (51%)	28/69 (41%)	1.65	0.82, 3.29	0.1581
Week 4	36/65 (55%)	30/68 (44%)	1.68	0.84, 3.36	0.1438
Follow-up	28/64 (44%)	24/71 (34%)	1.89	0.87, 4.10	0.1089
CGIC responders [d]					
Placebo run-in	17/68 (25%)	16/71 (23%)	1.29	0.57, 2.90	0.5420
Week 2	35/67 (52%)	29/69 (42%)	1.71	0.84, 3.49	0.1377
Week 4	35/65 (54%)	30/68 (44%)	1.64	0.81, 3.31	0.1670
Follow-up	29/65 (45%)	29/71 (41%)	1.41	0.66, 3.02	0.3720
Adjusted mean change from baseline for secondary efficacy variables for low back pain					
Variable **Time point**	**GW856553** **N=68**	**Placebo** **N=71**	**Adjusted mean difference**	**95% CI**	**P-value [a]**
PI-NRS					
Week 1	-0.76	-0.53	-0.23	-0.53, 0.07	0.1302
Week 2	-0.98	-0.76	-0.22	-0.59, 0.16	0.2520
Week 3	-1.31	-0.85	-0.46	-0.90, -0.03	0.0379
Week 4	-1.39	-1.07	-0.32	-0.78, 0.15	0.1780
Follow-up	-1.18	-0.76	-0.42	-0.94, 0.09	0.1037
SF-MPQ Total Score [b]					
Week 2	-3.8	-2.8	ND	ND	ND
Week 4	-4.7	-3.6	ND	ND	ND
Follow-up	-3.2	-2.4	ND	ND	ND
SF-MPQ Affective Score [b]					
Week 2	-1.4	-1.0	ND	ND	ND
Week 4	-1.9	-1.1	ND	ND	ND
Follow-up	-1.4	-0.6	ND	ND	ND
SF-MPQ Sensory Score [b]					
Week 2	-2.4	-1.8	ND	ND	ND
Week 4	-2.8	-2.5	ND	ND	ND
Follow-up	-1.8	-1.9	ND	ND	ND
Oswestry Disability Index					
Week 4	-7.71	-2.92	-4.79	-8.15, -1.43	0.0055

Proportion of responders for low back pain					
Variable **Time point**	**GW856553** **N=68**	**Placebo** **N=71**	**Adjusted odds ratio**	**95% CI**	**P-value [a]**
≥30% reduction in PI-NRS					
Week 1	12/67 (18%)	11/71 (15%)	1.41	0.50, 3.97	0.5182
Week 2	18/68 (26%)	16/69 (23%)	1.38	0.53, 3.58	0.5132
Week 3	24/65 (37%)	18/69 (26%)	1.96	0.83, 4.60	0.1250
Week 4	25/65 (38%)	20/68 (29%)	1.63	0.73, 3.63	0.2309
Follow-up	19/57 (33%)	14/55 (25%)	1.72	0.67, 4.42	0.2611
≥50% reduction in PI-NRS					
Week 1	3/67 (4%)	2/71 (3%)	1.38	0.23, 8.15	0.7230
Week 2	6/68 (9%)	5/69 (7%)	1.18	0.35, 3.95	0.7887
Week 3	8/65 (12%)	7/69 (10%)	1.16	0.39, 3.46	0.7860
Week 4	12/65 (18%)	10/68 (15%)	1.26	0.50, 3.19	0.6292
Follow-up	7/57 (12%)	7/55 (13%)	1.06	0.33, 3.40	0.9250
PGIC responders					
Placebo run-in	16/66 (24%)	18/70 (26%)	1.01	0.46, 2.22	0.9856
Week 2	34/67 (51%)	25/68 (37%)	1.94	0.97, 3.85	0.0601
Week 4	34/65 (52%)	28/67 (42%)	1.60	0.80, 3.23	0.1870
Follow-up	26/64 (41%)	25/70 (36%)	1.48	0.69, 3.20	0.3131
CGIC responders					
Placebo run-in	14/68 (21%)	14/70 (20%)	1.18	0.50, 2.77	0.7114
Week 2	34/67 (51%)	24/68 (35%)	2.17	1.07, 4.42	0.0323
Week 4	33/65 (51%)	28/67 (42%)	1.58	0.78, 3.22	0.2068
Follow-up	29/65 (45%)	27/70 (39%)	1.57	0.74, 3.33	0.2413
Adjusted mean change from baseline for other efficacy variables					
Variable **Time point**	**GW856553** **N=68**	**Placebo** **N=71**	**Adjusted mean difference**	**95% CI**	**P-value [a]**
Sleep Interference Scale score					
Week 1	-0.89	-0.52	-0.36	-0.67, -0.06	0.0188
Week 2	-1.19	-0.74	-0.45	-0.80, -0.09	0.0136
Week 3	-1.29	-0.92	-0.37	-0.73, -0.02	0.0405
Week 4	-1.48	-1.13	-0.35	-0.78, 0.08	0.1109
POMS total score					
Week 2	-9.09	-0.10	-9.00	-16.24, -1.75	0.0153
Week 4	-12.45	-3.45	-9.00	-16.46, -1.55	0.0183
Time taken to complete 20m walk (s)					
Week 4	-0.91	-1.41	0.50	-1.27, 2.27	0.5768
Walking-associated pain					
Week 4	-0.39	-0.40	0.01	-0.33, 0.35	0.9551
SF-36 physical functioning					
Week 4	8.46	0.91	7.55	2.90, 12.20	0.0017
SF-36 bodily pain					
Week 4	12.31	5.82	6.49	1.09, 11.90	0.0190
SF-36 general health					
Week 4	2.70	-1.90	4.60	0.33, 8.87	0.0351
SF-36 mental health					
Week 4	4.01	2.54	1.47	-2.90, 5.85	0.5060
SF-36 role - emotional					
Week 4	8.63	-1.41	10.04	1.84, 18.24	0.0169

SF-36 role - physical Week 4	6.82	2.76	4.06	-2.64, 10.76	0.2324
SF-36 social functioning Week 4	12.52	2.29	10.23	3.69, 16.78	0.0024
SF-36 vitality Week 4	8.33	0.87	7.47	2.22, 12.71	0.0057
SF-36 physical component Week 4	3.13	0.61	2.52	0.78, 4.25	0.0048
SF-36 mental component Week 4	2.99	0.58	2.41	0.09, 4.74	0.0420

a. P-values were not adjusted for multiple comparisons.
b. Adjusted mean change from baseline.
c. Unadjusted mean change from baseline.
d. 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; POMS, Profile of Mood States; SF-MPQ, Short-form McGill Pain Questionnaire.

Pharmacokinetic Results:
256 plasma GW856553 concentration records were collected from 67 subjects, of which 1 was not reportable. No non-quantifiable concentrations were observed. Compliance based on the degree of non-quantifiable concentrations, and that observed GW856553 concentrations were generally within the predicted range, indicating that compliance within the study was very high. There was no evidence for an association between greater reduction in PI-NRS scores and 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.

	GW856533 N=68	**Placebo N=71**
Placebo run-in		
Number of subjects with AEs, n (%)	12 (18)	13 (18)
Most frequent AEs (≥2% in any group)		
Headache	6 (9)	8 (11)
Diarrhoea	1 (1)	2 (3)
SAEs, n (%) [n(%) considered by the investigator to be related, possibly related, or probably related to study medication]	0 (0) [0 (0)]	0 (0) [0 (0)]
Double-blind treatment period		
Number of subjects with AEs, n (%)	34 (50)	23 (32)
Most frequent AEs (≥2% in any group)		
Headache	8 (12)	7 (10)
Diarrhoea	4 (6)	0 (0)
Pyrexia	3 (4)	0 (0)
Nasopharyngitis	2 (3)	4 (6)
Fatigue	2 (3)	1 (1)
Dysgeusia	2 (3)	0 (0)
Gastritis	2 (3)	0 (0)
Nausea	2 (3)	0 (0)
Pharyngitis	2 (3)	0 (0)
Constipation	1 (1)	3 (4)
Gastroenteritis	1 (1)	2 (3)
Vomiting	0 (0)	2 (3)
SAEs, n (%) [n(%) considered by the investigator to be related, possibly related, or probably related to study medication]	0 (0)	0 (0)
Follow-up		
Number of subjects with AEs, n (%)	8 (12)	6 (8)

Most frequent AEs (≥2% in any group)		
None		
SAEs, n (%) [n(%) considered by the investigator to be related, possibly related, or probably related to study medication]	2 (3) [0 (0)]	0 (0) [0 (0)]
Supraventricular tachycardia	1 (1) [0 (0)]	0 (0) [0 (0)]
Pulmonary embolism[a]	1 (1) [0 (0)]	0 (0) [0 (0)]
a. On autopsy this subject was also found to have lymphoma, which was classified as an SAE. The lymphoma was an incidental finding to the pulmonary embolism established at autopsy and the start date was unknown.		

Conclusion:
The adjusted mean change from baseline in PI-NRS score at Week 4 of the double-blind treatment period (primary endpoint) was -1.91 and -1.55 units in GW856553 and placebo groups, respectively, and the adjusted mean treatment difference of -0.36 was not statistically significant. During the double-blind treatment period, adverse events were reported by 34 (50%) subjects in the GW856553 group and 23 (32%) subjects in the placebo group. The most frequently reported adverse events were headache and diarrhoea in the GW856553 group and headache and nasopharyngitis in the placebo group. One death was reported in the GW856553 group during the follow-up phase (due to pulmonary embolism identified at autopsy; evidence of arteriosclerosis and severe generalised malignant lymphoma of unclear type was also found on autopsy). One non-fatal serious adverse event of supraventricular tachycardia was also reported in the GW856553 group during the follow-up phase. No non-quantifiable GW856553 plasma concentrations were observed (from 67 subjects) and GW856553 concentrations were generally within the predicted range, indicating that compliance within the study was very high. Overall, there was no evidence of a greater reduction in PI-NRS scores with higher GW856553 plasma concentrations.