Synopsis

Identifier: HM2008/00555/00 **Study Number:** MKN106762

Title: A double-blind placebo-controlled study of the efficacy and safety of the P38 Map Kinase inhibitor SB681323 in patients with neuropathic pain following nerve trauma

Investigators:

Investigator Number	Principal Investigator	Site details
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Publications: None at the time of this report

Study period:

Initiation Date: 19 Jul 2006

Completion Date: 11 Aug 2008

Phase of development: II

Objectives: The primary objective was to investigate the effect of SB681323 on the clinical signs of neuropathic pain in patients with nerve trauma and/or compression.

Secondary objectives were:

- To investigate the effect of SB681323 on experimental psychophysical measures of sensitisation in pain pathways in patients with nerve trauma and/or compression,

- To investigate the effect of SB681323 on specific measures of the Transient Receptor Potential Cation Channel (TRP, including TRPV1) pathways in patients with nerve trauma and/or compression,
- To investigate the value of these additional exploratory endpoints for future studies in neuropathic pain patients, and
- To assess the safety of SB681323 in patients with neuropathic pain.

Methodology: This study was designed to examine the efficacy and safety of SB681323 in patients with chronic neuropathic pain due to nerve trauma or compression. It was a double-blind, placebo controlled two-period cross-over study. Screening involved quantitative sensory testing (QST) and neurophysiological tests to select patients with functional evidence of nerve compression. After enrolment and initial assessments, patients were randomised to receive oral SB681323 or matching placebo for 14 days, before crossing over to receive the other study treatment (placebo or SB681323) in a second 14-day session. There was a washout period of two to four weeks between treatment sessions. Subjects attended for a follow-up visit approximately 28 days after the last dose. Patients visited the Unit on Days 1, 7 and 14 of each treatment session for safety and efficacy assessments, average daily intensity was recorded on a diary card.

In the original protocol, SB681323 was administered twice daily, 2.5 mg in the morning and 5 mg in the evening, to give a total daily dose of 7.5 mg. Following the availability of additional repeat dosing data in healthy volunteers supporting higher doses, a protocol amendment was implemented to increase the dose to 15 mg/day administered as two equal doses of 7.5 mg. All primary analyses compare SB681323 15 mg/day (7.5 mg twice-daily) vs. placebo, and only the primary objective was explored using all patients who received any dosage of SB681323.

Patients were allowed to continue medication for their neuropathic pain provided it had not been changed for at least four weeks before randomisation and remained unchanged over the course of the study, and if it was not listed as a prohibited medication. The use of a rescue medication (paracetamol, up to 2 g per day) was allowed if pain became intolerable. Patients were asked to refrain from taking the rescue within 24 h of a treatment visit.

Number of patients: It was planned to recruit sufficient numbers of patients in order to obtain a minimum of 40 evaluable patients. Fifty patients were randomised and 43 patients completed the study. Overall, 46 patients received at least one dose of placebo, three patients received at least one dose of SB681323 7.5 mg/day and 44 received at least one dose of SB681323 15 mg/day. One patient was randomised but never received a single dose of study medication.

Patient Disposition and Demographics:

Number of Patients	Total
Number of patients planned, N:	40
Number of patients enrolled, N:	51
Number of patients randomised, N:	50
Number of patients included in All patients (safety) population, n (%):	50
Number of patients completed as planned, n (%):	43 (86)
Number of patients withdrawn (any reason), n (%):	7 (14)
Number of patients withdrawn for SAE, n (%):	0
Number of patients withdrawn for AE, n (%):	4 (8) 2 active; 2 placebo
Other reasons for patient withdrawal, n (%) Withdrew consent Protocol violation	3 (6) 2 (4) 1 (2)
Demographics	
Age in Years, Mean (Range)	55.1 (28 – 78)
Sex, n (%)	
Female:	24 (48)
Male:	26 (52)
BMI, Mean (Range)	27.3 (19.1 – 33.2)
Height, Mean (Range)	168.5 (151 – 188)
Weight, Mean (Range)	77.7 (54.0 – 101.6)
Ethnicity, n (%)	
Hispanic or Latino:	0
Not Hispanic or Latino:	50 (100)
Race, n (%)	
White – White/Caucasian/European Heritage	49 (98)
White – Mixed race	1 (2)

Source data: Table 9.01, Table 9.02 and Table 9.03

Medical condition classification at baseline	
Carpal tunnel syndrome, n (%)[1]	5 (10)
Nerve trauma, n (%)[2]	13 (26)
Radiculopathy, n (%)[3]	32 (64)

Source data: Table 9.05

1. n = 5 (Australia)
2. n = 3 (Australia), n = 10 (UK)
3. n = 9 (Australia), n = 20 (Russia), n = 3 (UK)

Diagnosis and main criteria for inclusion: Male or female patients aged 18-80 years with a diagnosis of peripheral neuropathic pain which was either:

- Focal neuropathic pain related to nerve injury caused by trauma or surgery not associated with ongoing infection,

- Pain associated with lumbo-sacral radiculopathy; patients with radiculopathy were only included if they had pain radiating to or below the knee and had loss of small fibre function as indicated by quantitative sensory testing (change from thermode baseline temperature of either > 9.6°C for warm sensation or > 5.6 °C for cool sensation in L4, L5 or S1 dermatomes) [Quraishi, 2004], or
- Carpal tunnel syndrome (CTS); patients with CTS were only included if there was evidence of loss of large and/or small fibre function (confirmed by an electrophysiological nerve conduction examination or by quantitative sensory testing - change from thermode baseline temperature of either > 5.2 °C for warm sensation or >4.5 °C for cool sensation - in median nerve territory).

The location of pain had to be consistent with the area innervated by the affected nerve(s), with or without other sensory symptoms in the affected area; pain had to be of at least three months duration. Baseline pain intensity score was to average ≥ 4 during the three days prior to randomisation (as reported on the 11-point pain intensity numerical rating scale). For CTS patients, peak daily pain was to be ≥ 4 for at least 3 days prior to randomisation. [redacted] All of the average daily pain intensities were ≥ 4 therefore the peak pain was by definition also ≥ 4. Patients who had received nerve blocks or steroid injections for neuropathic pain may have been included if their most recent nerve block was at least 4 weeks prior to randomisation.

Body weight had to be ≥ 50 kg (110 lbs) for men and ≥ 45 kg for women, with a Body Mass Index (BMI) of 18.5-35kg/m^2. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had to be within normal limits at screening and patients had to have a QTc(b) of < 450 msec, or < 480 msec for patients with bundle branch block at screening.

Treatment administration: SB681323 (as the tosylate salt SB681323T) tablets 2.5 mg (batch numbers 071132100, 071143795, 061116225 and 071142203) and 5 mg (batch numbers 071132101, 071143797, 061116226 and 071142204) and matching placebo (batch numbers 071132102, 071143798, 061116227 and 071142206) were supplied by GlaxoSmithKline Pharmaceuticals as aqueous, film-coated 9 mm, white, round tablets in double-blind, labelled bottles. The patient recorded the date, time and number of tablets administered in the diary card and information was transcribed to the case report form.

Criteria for evaluation: The primary endpoint was the average daily pain score based on the 11 point pain intensity numeric rating scale (PI-NRS) (0 = no pain, 10 = worst pain imaginable) over Week 1 and Week 2 of the treatment.

Secondary endpoints were:

- Current pain intensity (CPI) assessment whilst in the clinic,
- Patient's global impression of change,
- Physician's global impression of change,
- Use of rescue medication (Week 1 and Week 2),

- Sensory thresholds (warm perception, heat pain, cold perception, cold pain) in the affected and control area as assessed by quantitative sensory testing, and
- Area and intensity of static (assessed with a von Frey hair) and dynamic (assessed with a foam brush) touch allodynia (when present).
- Safety endpoints were adverse events, vital signs (blood pressure and heart rate), 12-lead electrocardiogram and safety laboratory tests (haematology, clinical biochemistry, urinalysis, pregnancy test).

Optional endpoints conducted at one site only (Professor Anand, investigator number 065584) were:

- Evoked potentials in response to pulses of noxious heat (contact heat-evoked potential stimulator: CHEPS) in the affected and control (mirror image site) area, and
- Capsaicin and heat receptor TRPV1 immunoreactivity and mechanism-related markers (NGF, CGRP) in skin biopsies if patients were proceeding to surgery.

Statistical methods: The sample size of 40 patients was based on feasibility. However, based on a between-patient standard deviation of 1.85 for change from baseline in pain scores from study A1A20004 (a placebo-controlled parallel group study in patients with peripheral neuropathic pain) and a sample size of 40 patients, a minimum difference of 1.3 for SB681323 relative to placebo could be detected with at least 80% power, using a type 1 error rate of 5%.

Final analyses for the primary endpoint: Due to an error in recording the correct information on Days 1, 7 and 14 at some of the sites, the primary endpoint over Week 1 and Week 2 of the treatment, was calculated as the mean of the average daily pain scores of Days 2 to 6 inclusive for Week 1, and the mean of Days 8 to 13 inclusive for Week 2.

The baseline average daily pain score was calculated as the mean of the average daily pain scores collected on the three days prior to each dosing period. The baselines fitted in the primary statistical model were the average of the two baselines and the adjusted baseline, which was calculated as the period baseline minus the average of the two baselines.

A mixed model repeated measures (MMRM) analysis was performed to compare the pain scores between treatment groups, with period, treatment, visit, country, diagnostic category, baseline, treatment by week and baseline by week interactions fitted as fixed effects, and patient fitted as a random effect. Visit was also used as the repeated effect.

As a further exploratory analysis of the primary endpoint, a similar statistical analysis was performed including all available data collected for each patient and all time points. Therefore for those patients where average daily pain was recorded on Days 1, 7 and 14, their average pain scores for Weeks 1 and 2 were calculated as the average of Days 1 to 7 and Days 8 to 14, respectively. This was done to assess whether the change in endpoint calculation had any effect on the result of the statistical analysis.

Final analysis for the secondary endpoints:

Current Pain Intensity: The CPI baseline was calculated as the mean of the average daily pain scores collected on the three days prior to each dosing period, the same baseline as used for the primary endpoint. A MMRM analysis was performed with period, treatment, visit, country, diagnostic category, baseline, treatment by week and baseline by week interactions as fixed effects, and patient as a random effect. Visit was also used as the repeated effect. CPI was recorded on Days 1, 7 and 14, however Day 1 was not included in the statistical model.

Quantitative Sensory Threshold: Baselines for quantitative sensory threshold data in both the affected and controlled areas were recorded pre-dose on Day 1 of each treatment period, and post-dose assessments were recorded on Day 14. A mixed model analysis of variance (ANOVA) was performed on each of the sensory tests in both sites, except for cold pain. The fixed terms in the ANOVA were period, treatment, baseline and diagnostic category. The average of the two baselines as well as the adjusted baseline was fitted as per the primary analysis. Patient was fitted as a random effect.

An ANOVA model was unable to be fitted for the cold pain threshold, as the assumptions of normality were violated and so a non-parametric McNemar's test was performed. This was performed by calculating a 2x2 contingency table of the frequencies where a patient's quantitative sensory threshold increased or decreased for each treatment period.

Area and Intensity of Static and Dynamic Allodynia: Baseline areas of static and dynamic allodynia were recorded pre-dose on Day 1 for both treatment periods for all patients where allodynia was present (i.e. if a patient had a recorded baseline area for Period 1 greater than zero cm^2). This was determined independently for static and dynamic allodynia. Post-dose assessments were performed in the Unit after dosing on Day 14.

McNemar's test was performed on both the area of static and dynamic allodynia. This was due to the modelling assumptions for an ANOVA being violated. As a sensitivity analysis an ANOVA model was run for both sets of data, including and excluding patients who were statistical outliers. The exclusion of statistical outliers satisfied modelling assumptions surrounding an ANOVA, however there was no clinical reason for the exclusion of these patients.

Baseline pain intensities of static and dynamic allodynia were recorded pre-dose on Day 1 for both treatment periods for all patients where allodynia was present (i.e. if a patient had a recorded pain intensity for Period 1 greater than zero cm^2, and a recorded baseline area for Period 1 greater than zero cm^2). This was determined independently for static and dynamic allodynia. Post-dose assessments were performed in the Unit after dosing on Day 14.

A mixed model ANOVA was performed for intensity of both static and dynamic allodynia, however, there were low patient numbers for both of these tests. This was due to the site in Russia not collecting any pain intensities of allodynia, and allodynia not being present in a number of patients where it was being collected. The fixed terms in the ANOVA were period, treatment, baseline and diagnostic category. The averages of the

two baselines as well as the adjusted baseline were fitted, as per the primary analysis. Patient was fitted as a random effect.

Global Impression of Change and Rescue Medication: Data for Days 7 and 14 of patient's and physician's global impression of change and the use of rescue medication were listed, summarised and graphically presented only.

Optional Endpoints: All optional endpoints were listed only due to a small sample size.

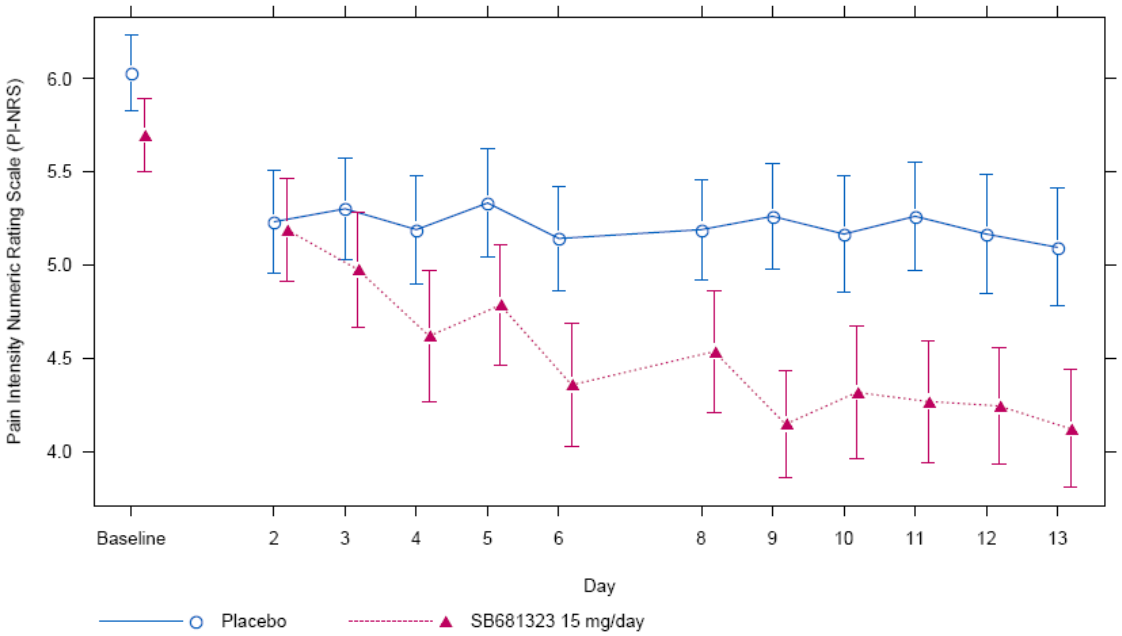
Safety Endpoints: All safety data were listed and summarised. Individual and mean profile plots of liver function tests were also produced.

Changes in the planned analysis: A number of additional efficacy outputs were produced. In addition to the planned statistical analyses, it was decided to perform an analysis of active drug versus placebo for the primary endpoint. Included in the active drug treatment arm were all patients who received dosing of SB681323. Three patients were randomized and received SB681323 7.5 mg before a protocol amendment increased the dosage to 15 mg/day. The same statistical analysis was conducted as for the primary endpoint.

A responder analysis was planned and was originally set to class a patient as a responder if they had a 35% or 50% reduction in their average daily pain score for week two. It was subsequently decided that a 30% and 50% responder rate was more appropriate as these are the standard pain responder rates used for the majority of pain clinical trials.

Efficacy: The 'Intent-to-Treat' (ITT) population consisted of all randomised patients who received at least the first dose of study medication and had at least one post-treatment efficacy assessment. The statistical analyses were performed on patients in the ITT population who were randomised to receive SB681323 15 mg / day and placebo. The diagnostic category of a patient was largely confounded with country. For example, all patients from Russia were radiculopathy patients, all carpal tunnel syndrome patients were from Australia and ten out of thirteen patients with peripheral nerve injury were from the UK. Therefore it was not possible to determine whether there was a country or a diagnostic effect present in this study.

Average daily pain score: The plot below shows the average daily pain intensities and standard error bars for subjects in the ITT population. This plot does not take into account the period in which the subjects received each regimen, however a clear separation can be seen between the daily responses for the second week of dosing whilst on active and placebo.



Source data: Figure 10.129

A summary of the primary statistical analysis of the average daily PI-NRS score for Weeks 1 and 2, calculated as the average of Days 2 to 6 and Days 8 to 13, respectively, is shown in the table below.

Summary of Repeated Measures Analysis of Average Daily Pain Intensity Numeric Rating Scale Score (Adjusted for Baseline, Baseline*Week, Country & Diagnostic Category)

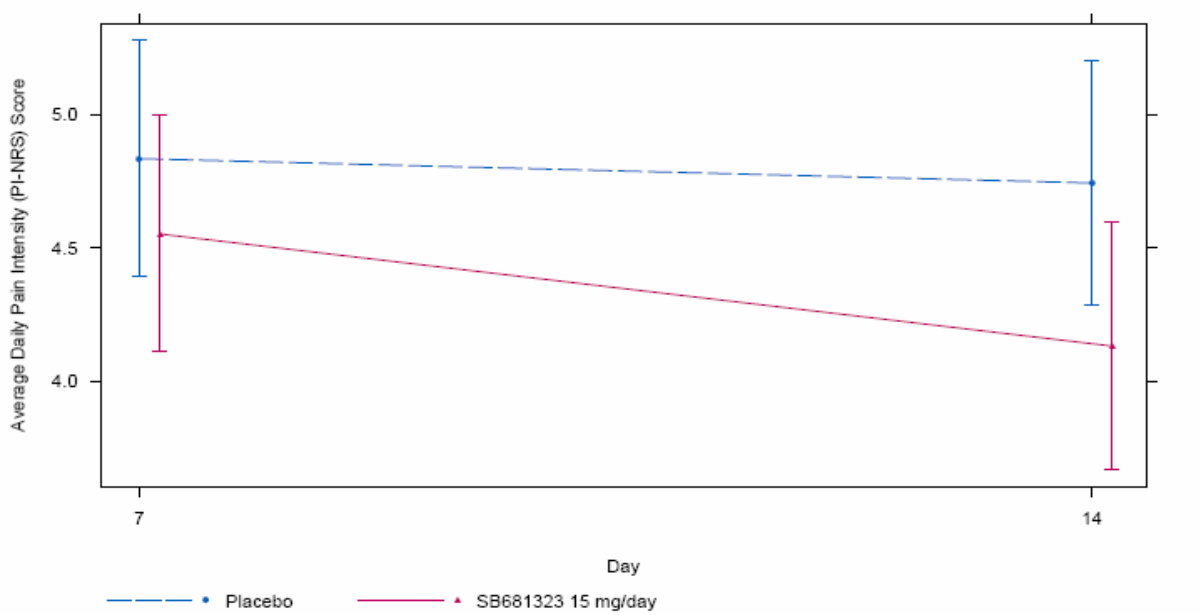
Visit	Adjusted mean SB681323 15 mg/day / Placebo		Adjusted mean difference (SB681323 15 mg/day – Placebo)	95% CI (lower, upper)	p-value	Within-patient Variance	Between-patient variance
Overall*	4.32	4.86	-0.54	(-0.97, -0.11)	0.0151	1.079	1.394
Week 1	4.57	4.85	-0.28	(-0.74, 0.18)	0.2244	0.939	1.253
Week 2	4.07	4.87	-0.80	(-1.33, -0.28)	0.0034	1.22	1.535

Source data: Table 10.3 n = 45 to 46 on placebo and n = 41 to 43 on SB681323
* calculated using both Week 1 and Week 2 endpoint data

The table shows the results of the MMRM analysis. The adjusted mean difference provides the best estimates of the true difference between SB681323 15 mg/day and placebo and the 95% confidence interval (CI) provides plausible ranges for the observed difference. A negative point estimate indicates a benefit of treatment.

On average there was a reduction of 0.28 in the average daily PI-NRS observed for SB681323 15 mg day compared to placebo in Week 1, which was not a statistically significant reduction. However, for Week 2, the primary time point of interest, there was a reduction in the average PI-NRS of 0.80 with SB681323 15 mg day compared to placebo. This result was statistically significant with a p-value of 0.0034, and the 95% CI showed a reduction of between 0.28 and 1.33 in favour of the active drug. The overall adjusted mean difference showed a reduction of 0.54 with the 95% CI showing a reduction for SB681323 of 0.11 to 0.97.

The least square means (± 95% CI) differences between SB681323 and placebo for both time points are shown in the figure below.



Source data: Figure 10.9

Additional Analyses: This analysis included all patients who received either dosage of SB681323 compared to placebo. A summary of the primary statistical analysis of average daily PI-NRS for Weeks 1 and 2, calculated as the average of Days 2 to 6 and Days 8 to 13, respectively, is shown in the following table.

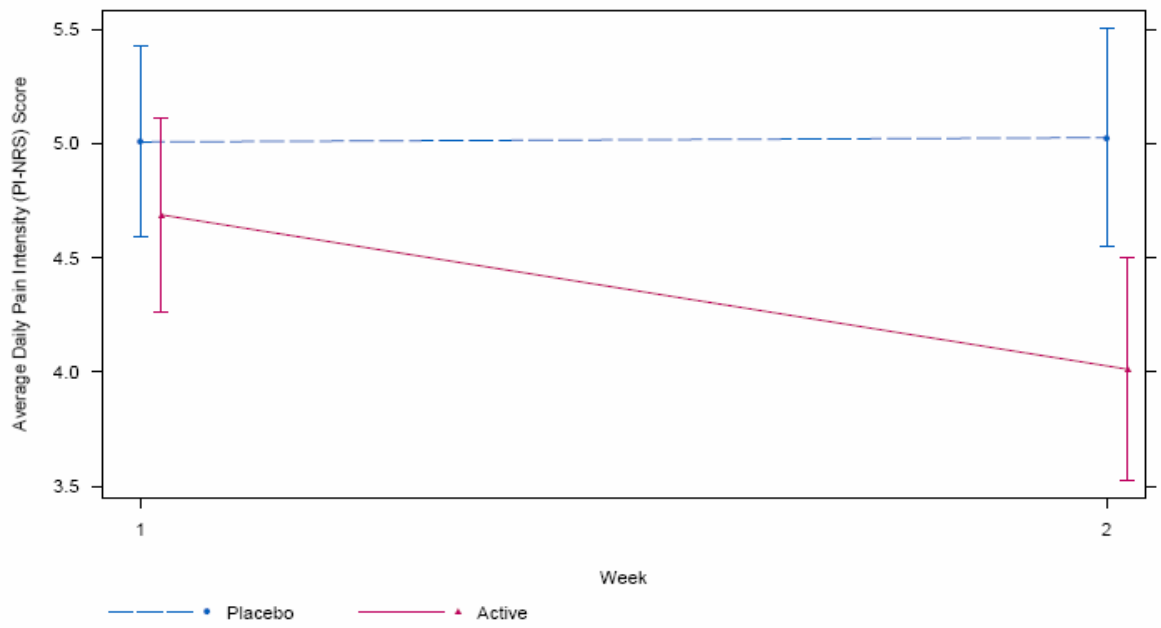
Summary of Repeated Measures Analysis of Average Daily Pain Intensity Numeric Rating Scale (PI-NRS) Score (Adjusted for Baseline, Baseline*Week, Country & Diagnostic Category) Active V Placebo

Visit	Adjusted mean SB681323 / Placebo		Adjusted mean difference (SB681323 – Placebo)	95% CI (lower, upper)	p-value	Within-patient Variance	Between-patient variance
Overall*	4.35	5.02	-0.67	(-1.09, -0.24)	0.0027	1.226	1.569
Week 1	4.69	5.01	-0.32	(-0.76, 0.12)	0.1548	0.949	1.292
Week 2	4.01	5.03	-1.01	(-1.57, -0.46)	0.0005	1.504	1.846

Source data: Table 10.220 n = 45 to 46 on placebo and n = 41 to 43 on SB681323
* calculated using both Week 1 and Week 2 endpoint data

On average there was a reduction in the average daily PI-NRS of 1.01 on SB681323 compared to placebo at Week 2. This result was statistically significant, with a p-value of 0.0005 and 95% CI of 0.46 to 1.57 in favour of the active drug. A reduction of 0.32 was also observed for Week 1, but was not statistically significant. The overall adjusted mean difference showed a reduction of 0.67 with 95% CI showing a reduction for SB681323 compared to placebo of 0.24 to 1.09.

The figure below presents the least square means (± 95% CI) differences between SB681323 versus placebo from the model, for both time points.



Source data: Figure 10.128

The plot shows the same pattern as was observed from the primary statistical analysis. A clear reduction in the average daily PI-NRS was reported by patients whilst on SB681323, whereas there was a very small change occurring for patients whilst on placebo.

Average daily pain score by diagnosis: A summary of the mean of the average daily pain score at baseline, Day 7 and Day 14, by diagnostic category and treatment is shown in the table below:

Diagnostic category	Treatment	Time point, Mean (standard deviation) PI-NRS		
		Baseline*	Week 1	Week 2
Carpal Tunnel Syndrome	Placebo (N = 5)	5.6 (1.36)	4.1 (1.91)	4.0 (2.32)
	SB681323 15 mg/day (N = 4)	5.7 (1.61)	2.7 (1.70)	2.3 (1.42)
Nerve trauma	Placebo (N = 12)	6.3 (1.64)	5.4 (2.05)	5.2 (2.18)
	SB681323 15 mg/day (N = 10)	5.8 (2.13)	4.9 (2.39)	4.2 (2.48)
Radiculopathy	Placebo (N = 29)	6.2 (1.28)	5.6 (1.52)	5.6 (1.47)
	SB681323 15 mg/day (N = 29)	5.7 (0.88)	5.0 (1.46)	4.6 (1.65)

Source data: Table 10.218

*The baseline was calculated using average daily pain intensity on the three days prior to dosing for all diagnostic categories

The largest decrease from baseline in average daily pain intensity score was seen in patients who had carpal tunnel syndrome and were treated with SB681323, although the number of patients was low (only 4 patients in the active treatment group) and so the results should be treated with caution (Source data: Table 10.218). The largest difference between Day 7 (end of Week 1) and Day 14 (end of Week 2) was seen in patients with nerve trauma.

A summary of the sub-group analysis for nerve trauma subjects average daily PI-NRS for Weeks 1 and 2, calculated as the average of Days 2 to 6 and Days 8 to 13, respectively, is

shown in the following table. Subjects on either dose of SB681323 were pooled together for the analysis. Only 13 subjects were included in this analysis and the following results should be interpreted with caution.

Summary of Repeated Measures Analysis of Average Daily Pain Intensity Numeric Rating Scale (PI-NRS) Score (Adjusted for Baseline, Baseline*Week) (Average of Weeks 1 (Days 2-6) and 2 (Days 8-13)) Peripheral Nerve Injury Subjects Only

Visit	Adjusted mean SB681323 / Placebo		Adjusted mean difference (SB681323 – Placebo)	95% CI (lower, upper)	p-value	Within-patient Variance	Between-patient variance
Overall*	4.86	5.13	-0.27	(-1.25, 0.71)	0.5613	1.607	2.128
Week 1	5.36	5.16	0.20	(-0.81, 1.21)	0.6590	0.901	1.422
Week 2	4.35	5.09	-0.74	(-2.17, 0.68)	0.2874	2.314	2.834

Source data: Table 10.241

* calculated using both Week 1 and Week 2 endpoint data

On average there was a reduction in the average daily PI-NRS of 0.74 on SB681323 compared to placebo at Week 2 with the 95% CI from -2.17 to 0.68.

A summary of the sub-group analysis for radiculopathy subjects average daily PI-NRS for Weeks 1 and 2, calculated as the average of Days 2 to 6 and Days 8 to 13, respectively, is shown in the following table. Subjects on either dose of SB681323 were pooled together for the analysis. Only 31 subjects were included in this analysis and the following results should be interpreted with caution.

Summary of Repeated Measures Analysis of Average Daily Pain Intensity Numeric Rating Scale (PI-NRS) Score (Adjusted for Baseline, Baseline*Week, Country) (Average of Weeks 1 (Days 2-6) and 2 (Days 8-13)) Radiculopathy Subjects Only

Visit	Adjusted mean SB681323 / Placebo		Adjusted mean difference (SB681323 – Placebo)	95% CI (lower, upper)	p-value	Within-patient Variance	Between-patient variance
Overall*	4.74	5.32	-0.58	(-1.12, -0.04)	0.0371	1.075	1.290
Week 1	5.02	5.28	-0.25	(-0.83, 0.32)	0.3778	0.908	1.123
Week 2	4.46	5.36	-0.90	(-1.58, -0.23)	0.0102	1.243	1.458

Source data: Table 10.239

* calculated using both Week 1 and Week 2 endpoint data

On average there was a reduction in the average daily PI-NRS of 0.90 on SB681323 compared to placebo at Week 2 with the 95% CI from -1.58 to -0.23.

Responder analysis: The following table summarises the number of patients who showed a 30% and 50% response for PI-NRS at Week 2, by diagnostic category and treatment.

Treatment	Diagnostic category, PI-NRS response rate at Week 2, number (%) of patients							
	Nerve trauma		CTS		Radiculopathy		Overall	
	30%	50%	30%	50%	30%	50%	30%	50%
Placebo	3/12 (25)	2/12 (17)	2/5 (40)	2/5 (40)	4/28 (14)	0/28 (0)	9/45 (20)	4/45 (9)
SB681323 7.5 mg/day	2/3 (67)	2/3 (67)	-	-	-	-	2/3 (67)	2/3 (67)
SB681323 15 mg/day	3/9 (33)	3/9 (33)	4/4 (100)	3/4 (75)	8/28 (29)	5/28 (18)	15/41 (37)	11/41 (27)

Source data: Table 10.13

The overall proportion of patients with a 50% response rate at Week 2 was higher on SB681323 15 mg/day (27% of patients) than on placebo (9% of patients).

The summary of results from McNemar's test, for the number of 50% responders in the SB681323 15 mg/day and placebo treatment arms is shown in the following table.

Diagnostic Category	McNemar's P-Value	Exact McNemar's P-Value
Overall (N = 43)	0.011	0.021

Source data: Table 10.243

Significant differences were observed for the number of overall 50% responders with McNemar's test (p=0.011) and the Exact test (p=0.021). This shows that there is a significant difference between the 50% responder rates between SB681323 15 mg/day and placebo.

Current daily pain intensity: A summary of the repeated measures analysis of CPI for Days 7 and 14 is presented in the following table.

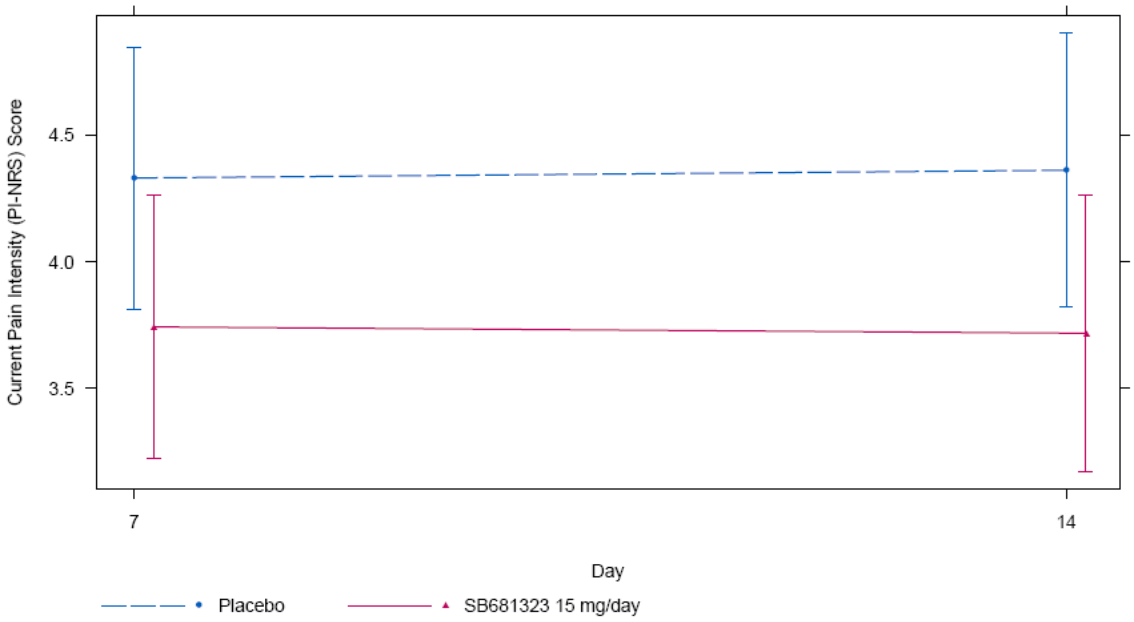
Summary of Repeated Measures Analysis of Current Pain Intensity Numeric Rating Scale (PI-NRS) Score (Day 7 and 14)

Visit	Adjusted mean SB681323 15 mg/day / Placebo		Adjusted mean difference (SB681323 15 mg/day – Placebo)	95% CI (lower, upper)	p-value	Within-patient Variance	Between-patient variance
Overall*	3.73	4.35	-0.62	(-1.10, -0.14)	0.0131	1.415	1.906
Day 7	3.74	4.33	-0.59	(-1.13, -0.05)	0.0342	1.294	1.785
Day 14	3.72	4.36	-0.64	(-1.23, -0.05)	0.0333	1.536	2.027

Source data : Table 10.22 n = 45 to 46 on placebo and n = 41 to 42 on SB681323
* calculated using both Week 1 and Week 2 endpoint data

On average, on Day 14, there was a reduction in daily CPI of 0.64 on SB681323 compared to placebo. This was a statistically significant reduction, with a 95% CI of -1.23, -0.05. There was a reduction of 0.59 in favour of SB681323 at Day 7, and a reduction of 0.62 overall. All three estimates were statistically significant at the 95% level.

The figure below presents the least square means (± 95% CI) differences between SB681323 and placebo for both time points.



Source data: Figure 10.12

The plot shows that the CPI stayed quite stable from Day 7 to Day 14 on both SB681323,and placebo.

Quantitative sensory threshold: The summary of the ANOVA for quantitative sensory tests, including cold pain, heat pain and warmth detection thresholds, in the affected area, is shown in the following table. For heat pain and warmth detection, higher temperature thresholds in the affected area would confirm the expected mechanism (inhibition of p38-mediated upregulation of the TRPV1 receptor on primary afferents), whereas for cold pain a lower temperature threshold in the affected area would be consistent with a similar mechanistic hypothesis (inhibition of p38-mediated upregulation of cold-sensitive TRP receptors on primary afferents). No such trends were expected in the control area.

Summary of ANOVA for Quantitative Sensory Testing (Adjusted for Baseline and Diagnostic Category) – Affected Area

Test	Adjusted mean SB681323 15 mg/day / Placebo		Estimate	95% CI (Lower,Upper)	p-value	Within-patient variance	Between-patient variance
Cold pain threshold	13.56	14.28	-0.72	(-3.09, 1.65)	0.5420	26.67	42.51
Heat pain threshold	46.32	46.03	0.29	(-0.51, 1.10)	0.4665	3.18	3.73
Warmth detection threshold	40.49	39.29	1.20	(0.06, 2.35)	0.0395	6.23	9.27

Source data : Table 10.36 n = 44 on placebo and n = 41 on SB681323 15 mg/day

On average, cold pain was detected at lower temperatures in the affected area whilst patients were on SB681323 15 mg/day compared to placebo. The estimate of -0.72 degrees centigrade difference was not significant, however, as can be seen from the CI (-3.09, 1.65) which includes zero.

On average, heat pain and warmth were detected at higher temperatures in the affected area whilst patients were on SB681323 15 mg/day, compared to placebo. The estimate for heat pain was not significant, but the estimate for the difference in the warmth detection threshold (1.20 °C) was significant (p = 0.04).

The summary of the ANOVA for quantitative sensory tests in the control area are shown in the following table.

Summary of ANOVA for Quantitative Sensory Testing (Adjusted for Baseline and Diagnostic Category) – Control Area

Test	Adjusted mean SB681323 15 mg/day / Placebo		Estimate	95% CI (lower, upper)	p-value	Within-patient variance	Between-patient variance
Cold pain threshold	16.40	15.79	0.61	(-2.00, 3.32)	0.6355	29.33	50.98
Heat pain threshold	44.47	45.23	-0.76	(-1.65, 0.13)	0.0912	3.82	7.10
Warmth detection threshold	37.57	37.87	-0.30	(-1.04, 0.44)	0.4172	2.63	7.32

Source data : Table 10.36 n = 44 on placebo and n = 41 on SB681323 15 mg/day

On average cold pain was detected at higher temperatures whilst patients were on SB681323 15 mg/day compared to placebo. The estimate of 0.61 °C difference was not significant.

The point estimate for heat pain in the control area shows that, on average, heat was detected at lower temperatures whilst patients were on SB681323 15 mg/day compared to placebo, and warmth was detected at lower temperatures whilst patients were on SB681323 15 mg/day compared to placebo. Neither of these estimates was significant.

The results from the McNemar's test, for non-normally distributed QST data, showed that no significant differences were observed between the SB681323 and placebo treatment arms for the cold detection threshold, at both affected and control sites. McNemar's p-value and the Exact p-value were insignificant for both the affected and control areas.

Area and intensity of static and dynamic allodynia: The summary of results from McNemar's test, for the area of static and dynamic allodynia, where allodynia was present, is shown in the following table.

Area Type	McNemar's P-Value	Exact McNemar's P-Value
Static Allodynia (n = 34)	0.4795	0.596615
Dynamic Allodynia (n = 19)	0.818546	1

Source data: Table 10.41 and Table 10.42

No significant differences were observed between the SB681323 15 mg/day and placebo treatment arms. McNemar's p-value and the Exact p-value are non-significant for both static and dynamic allodynia. The data were highly variable between patients, with a number of outlying values that were not plausible.

The results for the ANOVA for area of static allodynia showed an adjusted mean difference of -28.04 cm^2 in favour of SB681323 15 mg/day over placebo on exclusion of the statistical outliers. This result was not statistically significant.

The results for the ANOVA for area of dynamic allodynia showed an adjusted mean difference of 16.11 cm^2 in favour of placebo over SB681323 15 mg/day on exclusion of the statistical outliers. This result was not statistically significant.

The summary results from the ANOVA, for the intensity of static and dynamic allodynia are presented in the table below.

Summary of ANOVA for Intensity of Static and Dynamic Touch Allodynia
(Adjusted for Baseline & Diagnostic Category)

Test	Adjusted mean SB681323 15 mg/day / Placebo		Estimate	95% CI (lower, upper)	p-value	Within-patient variance	Between-patient variance
Static allodynia (n = 11)	3.69	4.78	-1.09	(-2.89, 0.71)	0.1901	2.579	4.496
Dynamic allodynia (n = 6)	3.93	5.64	-1.71	(-4.89, 1.46)	0.1845	1.642	1.642

Source data: Table 10.43 and Table 10.44

On average there was a reduction in the pain intensity of static allodynia of 1.09, and a reduction in the pain intensity of dynamic allodynia of 1.71, with SB681323 15 mg/day compared to placebo. The patient numbers involved in both of these parameters were very low and neither of these results was statistically significant.

Global Impression of Change and Rescue Medication: The patient's and physician's global impression of change on placebo and SB681323 15 mg/day at Day 14 are summarised in the following table.

	Global impression of change at Day 14, number of patients (%)			
	Patient's		Physician's	
	Placebo (n = 45)	SB681323 15 mg/day (n = 41)	Placebo (n = 45)	SB681323 15 mg/day (n = 41)
Very much improved	1 (2)	3 (7)	0 (0)	4 (10)
Much improved	4 (9)	10 (24)	4 (9)	8 (20)
Minimally improved	15 (33)	12 (29)	13 (29)	12 (29)
No change	23 (51)	16 (39)	27 (60)	17 (41)
Minimally worse	1 (2)	0 (0)	1 (2)	0 (0)
Much worse	1 (2)	0 (0)	0 (0)	0 (0)
Very much worse	0 (0)	0 (0)	0 (0)	0 (0)

Source data: Table 10.226 and Table 10.229

Overall, the patient's global impression of change showed that 25/41 (61%) of subjects condition had improved for patients on SB681323 15 mg/day and only 20/45 (44%) patients on placebo improved. The physician's global impression of change showed that 24/41 (59%) subjects condition had improved for patients on SB681323 15 mg/day and only 17/45 (38%) of patients on placebo.

The proportions of patients who used rescue medication were: no patients on SB681323 7.5 mg daily, 2/46 patients on placebo (4.3%) and 3/43 patients on SB681323 15 mg daily (7.0%) (Source data: Table 10.27).

Optional Endpoints: All optional endpoints were listed only and no conclusions were made, due to a small set of data.

Safety: The safety analysis was based on the 'All Patients' population which consisted of all patients who were randomised and received at least one dose of study medication. The overall numbers of patients reporting adverse events (AEs) and the most frequent AEs are summarised below:

	Placebo N = 46	SB681323 7.5 mg/day N = 3	SB681323 15 mg/day N = 44
Any AE, n (%)	23 (50)	2 (67)	20 (45)
Most Common AEs (≥ 2 subjects in any treatment group):			
Headache	8 (17)	1 (33)	9 (30)
Nasopharyngitis	3 (7)	0	0
Pharyngolaryngeal pain	2 (4)	1 (33)	1 (2)
Nausea	2 (4)	0	2 (5)
Diarrhoea	2 (4)	0	1 (2)
AEs related to investigational product:			
Any AE	9 (20)	0	4 (9)
Most common AEs related to investigational product (≥ 2 subjects in any treatment group)::			
Headache	2 (4)	0	3 (7)
Diarrhoea	2 (4)	0	0

Source data: Table 11.2 and Table 11.3

Two patients on placebo and two patients on SB681323 15 mg/day were withdrawn from the study due to AEs, all withdrawals occurred prior to the start of Period 2. One patient on SB681323 15 mg/day was withdrawn on Day 4 due to nausea, abdominal pain and weakness which were not thought by the investigator to be related to study drug but rather due to a suspected gastrointestinal infection. The nausea started on the first day of dosing, 6 h 10 min post-dose, abdominal pain and weakness started on Day 2. The other patient on SB681323 was withdrawn on Day 29 due to *Herpes zoster* rash, which started 16 days 21 h after starting SB681323 15 mg/day and 3 days 23 h after the last dose, and itchy eyes, which started 2 days later and resolved after 19 days (the outcome of the rash was 'recovering' at the end of the study). Neither the *Herpes zoster* rash nor the itchy eyes were thought by the investigator to be related to study medication.

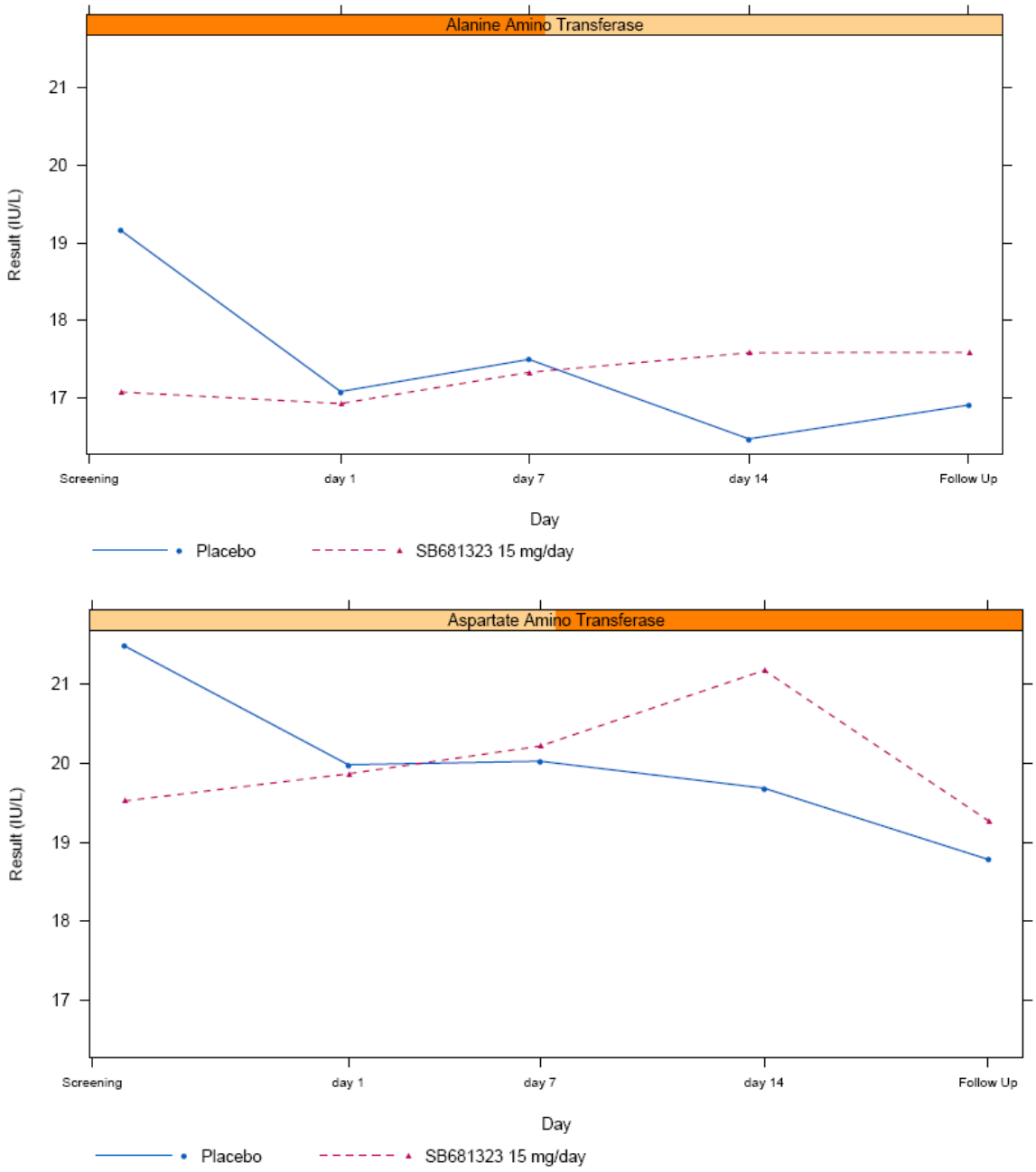
One patient on placebo was withdrawn due to facial oedema on Day 7, which occurred 10 h 30 min after the first dose and was suspected to be related to study drug, and another patient on placebo was withdrawn on Day 28 due to increased proteinuria that was reported on Day 6. This was not thought to be related to study drug and was concluded by the investigator to be due to a pre-existing condition, which was later confirmed by a consultant nephrologist.

Adverse events reported as related to treatment, in patients on SB681323 15 mg/day, were headache, dizziness, lethargy, constipation, vomiting, sweating and nervousness.

There were no deaths, non-fatal SAEs or pregnancies reported during this study. Frequency of mild and moderate AEs was similar on SB681323 and placebo, whereas there were more severe AEs reported on placebo. Severe AEs reported on placebo were headache, diarrhoea, nausea, vomiting, bronchitis, arthralgia, back pain, pain in the extremity and dysmenorrhoea, each reported in one subject. The only severe AE reported on SB681323 15 mg/day was toothache. The number (%) of patients with AEs at each level of intensity is shown by treatment in the following table:

AE intensity	Placebo N=46	SB 681323 7.5 mg/day N=3	SB681323 15 mg/day N=44
Mild	12 (26%)	1 (33%)	12 (27%)
Moderate	5 (11%)	1 (33%)	7 (16%)
Severe	6 (13%)	0	1 (2%)

AEs of special interest due to toxicological and class-related findings were abnormalities in liver function tests, muscle creatinine kinase, gastrointestinal symptoms suggestive of enterotoxicity (e.g. diarrhoea) and changes in red cell count. No changes in liver function tests (LFTs) were reported as AEs, only one LFT change, raised total bilirubin (34 umol/L: reference range 0-22 umol/L) was reported at follow-up, 36 days after the patient's last dose of SB681323. This patient was taking placebo in Period 1 and SB681323 in Period 2 and had normal liver enzymes and bilirubin throughout the study. One patient had raised creatine phosphokinase reported as an AE during the placebo session. Diarrhoea was reported in two patients during placebo treatment (one moderate; one severe) and one patient on SB681323 15 mg/day (mild). One patient on SB681323 15 mg/day had low haemoglobin on Day 14 of Period 2 (94 g/L, reference range: 120-156 g/L). Mean plots of ALT and AST are shown below. There were no trends for ALT and AST to increase to a level above the upper limit of normal during treatment with SB681323.



Overall, there were no clinically relevant abnormalities in laboratory data, vital signs or electrocardiogram data.

Conclusions:

- This study demonstrated a therapeutic benefit of SB681323 in patients with chronic pain associated with nerve injury or compression. Statistically significant improvements were observed on several endpoints following two weeks of treatment with SB681323 vs. placebo.
- At Week 2, the adjusted mean difference in the average daily pain intensity on the 11-point numeric rating scale was 0.80 in favour of SB681323 15 mg/day over

placebo. The 95% confidence interval around this point estimate was (-1.33, -0.28). The adjusted mean difference increased to -1.01 in favour of SB681323 when the same repeated measures model was applied to the full dataset of those patients who received any dose of study medication. This result was highly significant, with a confidence interval of (-1.57, -0.46).

- The current pain intensity at Day 7 and Day 14 was also statistically significantly lower on SB681323 15 mg/day than on placebo at the 5% level ($p = 0.03$).
- All three aetiological groups (peripheral nerve injury, carpal tunnel syndrome, radiculopathy) appear to have responded to the active treatment more than placebo.
- The overall proportion of patients with a 50% improvement from baseline at Week 2 was higher on SB681323 15 mg/day (27% of patients) than on placebo (9% of patients). As 50% improvement is deemed clinically important, this suggests that the treatment benefit was of clinical significance.
- On Day 14, the patient's global impression of change showed that their condition had improved (either very much, much or minimally) for 25/41 (61%) of patients on SB681323 15 mg/day and for 20/45 (44%) of patients on placebo. The physician's global impression of change closely reflected the patient's. Similar to the responder analysis, this suggests that the treatment benefit was of clinical significance.
- Quantitative sensory tests (cold and warmth detection thresholds and cold and heat pain thresholds) were analysed to assess mechanistic hypotheses on the p38-mediated upregulation of TRPV1 and cold-sensitive TRP receptors on affected primary afferents. In general, QST changes in the affected area were consistent with the proposed mechanisms but the treatment difference only reached significance for one endpoint (warmth detection threshold). No such trends were observed in the control area.
- Allodynia endpoints (area and intensity) were assessed as quantitative measures of central sensitisation. However, the presence of allodynia was not a recruitment requirement, and it was only present in a minority of patients. Areas of static and dynamic allodynia appeared highly variable and no significant treatment effects were observed. With the intensity of allodynia (both static and dynamic), there were trends in favour of SB681323, with a magnitude of treatment difference comparable to or greater than that for average daily pain; however, these differences were not statistically significant, likely due to low numbers of observations.
- SB681323 was well tolerated with no clinically relevant safety findings. There were no trends of concern in liver function tests or any other pre-defined safety markers of interest.

References:

Quraishi NA, Taherzadeh O, McGregor AH, Hughes SP, Anand P (2004) Correlation of nerve root pain with dermatomal sensory threshold and back pain with spinal movement in single level lumbar spondylosis. J Bone Joint Surg Br 86: 74-80.

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