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.: PXN110527
Title: Study PXN110527: The investigation of the efficacy and pharmacokinetics of gabapentin enacarbil (GEn/XP13512/GSK1838262) in subjects with neuropathic pain associated with post-herpetic neuralgia (PHN) who have had an inadequate response to gabapentin treatment.
Rationale: The primary purpose of study PXN110527 was to investigate the efficacy of a high (3600mg/day) dose versus a low (1200mg/day) dose of gabapentin enacarbil (GEn) in subjects with post-herpetic neuralgia (PHN) who have a history of an inadequate response to gabapentin treatment.
Phase: IIa
Study Period: 14 March 2008 to 27 July 2009
Study Design: This was a multicenter; randomized; double-blind; two-period crossover study
Centres: 35 centers randomized subjects: 8 centers in Germany (EU) and 27 centers in the USA (NA)
Indication: Post-herpetic neuralgia (PHN)
Treatment: Subjects were enrolled in a two week Baseline Period, which included treatment with 1800 mg/day Neurontin to confirm inadequate pain response at randomization. Subjects who met entry criteria were randomized to receive gabapentin enacarbil (either 1200 mg/day or 3600 mg/day in a 1:1 ratio) for Treatment Period 1 (28 days). Following completion of Treatment Period 1, all subjects received a dose of 2400 mg/day for 4 days during the Crossover Period, followed by an alternate fixed dose (either 3600 mg/day or 1200 mg/day) for Treatment Period 2 (28 days). Including pre-treatment and post-treatment periods, the maximum duration of the study was 19 weeks. Investigational product was supplied as a free acid formulated as an oral, extended release, white to off-white tablet containing gabapentin enacarbil 600 mg or matching placebo supplies. Subjects were to take the investigational product daily with food, and were to swallow the tablets whole with water, once in the morning and once in the evening. During the two week Baseline Period, all subjects received open-label commercial gabapentin 600 mg three times daily (TID, 1800 mg/day) supplied by GSK. Gabapentin elliptical film-coated 600 mg tablets were provided in 100-count bottles.
Objectives: The primary objective of the study was to investigate the difference between two doses of GEn (3600 mg/day versus 1200 mg/day) on pain intensity.
Primary Outcome/Efficacy Variable: Change from baseline in the mean 24-hr average pain intensity (API) score based on an 11-point Pain Intensity-Numerical Rating Scale (PI-NRS) at the end of 4 Weeks treatment using Last Observation Carried Forward (LOCF) data
Secondary Outcome/Efficacy Variable(s): Secondary endpoints were based on daily e-diary and clinic visit assessments. Change from baseline in the mean: night time average pain intensity (night-time is defined as the time between going to bed in the evening and rising in the morning), current pain intensity, night time worst pain intensity (worst pain is defined as the subject's assessment of their worst pain intensity), sleep interference (sleep interference is the subject's assessment of sleep interference due to pain). All recorded in the e-diary in the morning upon awakening. Change from baseline in the mean: day-time average pain intensity (day-time is defined as the time between rising in the morning and going to bed in the evening), day-time worst pain intensity. All recorded in the e-Diary in the evening before going to bed Proportion of responders (subjects who are "much improved" or "very much improved") on each of the Patient Global Impression of Change (PGIC) and Clinician Global Impression of Change (CGIC) questionnaires at each assessment. Proportion of subjects achieving various levels of percent reduction from baseline in the mean 24-hour average pain

intensity score at each week of treatment.
Quantity of rescue analgesia consumed at each week of treatment and post-treatment. Commercial acetaminophen 500 mg was provided as a rescue analgesic to be administered on an 'as needed' basis during any study period up to a maximum dose of 3000 mg (6 tablets) per 24-hour period, as instructed by the investigator. Subjects were requested not to take any rescue analgesic within 12 hours before a clinical visit.
Pharmacokinetics of GEn were also assessed.

Statistical Methods: The sample size calculation for this study was based on providing enough subjects to enable the detection of a treatment difference in the primary efficacy endpoint (change from baseline in mean 24-hour average pain intensity score assessed for the last week of each treatment period). Assuming within-subject standard deviation of 1.48 and a two-tailed t-test at an alpha level of 0.10 at least 78 subjects completing this two period crossover study would have provided 80% power to detect a treatment difference of 0.6 between the high dose (3600 mg/day) and the low dose (1200 mg/day) of gabapentin enacarbil. Therefore, assuming a 20% drop out rate prior to the end of the first week of Treatment Period 2, it was planned that a total of approximately 98 subjects would be randomized.

The Safety Population, used to assess safety endpoints, was composed of all randomized subjects who took at least one dose of investigational product.
The Intent-to-Treat (ITT) Population, primary population used to assess all efficacy endpoints, was composed of all randomized subjects who took at least one dose of randomized investigational product and provided at least one post-baseline efficacy measurement.
The PK analysis population did not include non-PK-compliant subjects, who were defined as subjects with at least one concentration < half of the 1st percentile of the concentrations observed at steady state.

Last observation carried forward (LOCF) approach was used to handle the missing data for the primary and secondary efficacy endpoints.
Continuous primary and secondary efficacy endpoints were analysed using a repeated measures mixed model (ANCOVA) with treatment and period as fixed effects and with baseline body mass index, baseline 24-hour average pain intensity score, and centre grouping as covariates and specified a repeated statement with unstructured covariance matrix to manage subjects as a source of random variability. The binary endpoints were analysed using a generalized estimating equation (GEE) procedure, with treatment and period as fixed effects in the model and with baseline BMI as a covariate, using the logit link function.

Study Population: For the purpose of this study, PHN was defined as pain persisting for ≥3 months after healing of the shingles rash. This study recruited subjects who were ≥18 years of age at screening, with a documented medical diagnosis of PHN of at least three months duration prior to screening. Prior to screening subjects were required to have a demonstrated history of an inadequate response (as determined by the investigator) to at least 1800 mg/day of gabapentin. Prior history of treatment with gabapentin included current treatment at 1800mg/day (2 weeks) or prior treatment with at least 1800mg/day for 4 weeks. With either of these scenarios, subjects could also have been treated with pregabalin monotherapy (150-300mg/day for at least 4 weeks) and had an inadequate response.. Subjects who in the investigators' judgment, had shown no response to previous treatment with either gabapentin (≥1800 mg/day) or pregabalin (150-300 mg/day) taken for at least 4 weeks since the diagnosis of PHN were not eligible for participation in the trial. Between screening and randomization all subjects received 1800 mg/day Neurontin® (gabapentin) to confirm an inadequate response prior to randomization. Randomized subjects were required to have a mean baseline 24-hour average pain intensity score based on an 11-point Pain Intensity Numeric Rating Scale (PI-NRS) of at least 4.0, calculated using the mean of the daily pain scores (based on at least 4 assessments) reported during the 7 days prior to randomization. The study enrolled 138 subjects into the Neurontin treatment period and 98 were subsequently randomized.

Subjects with chronic pain not associated with PHN were excluded unless they met all of the following criteria: pain located at a different region of the body, pain intensity not greater than the pain intensity of the PHN and the subject could assess PHN pain independently of other pain conditions.

Since the concentration of gabapentin, the active moiety of gabapentin enacarbil, in the serum is increased with reduced renal function, subjects with a creatinine clearance (CrCl) of <60 mL/min (estimation of CrCl by Cockroft and Gault Method) or renal dysfunction requiring hemodialysis were excluded.

Number of Subjects:	**GEn 1200 mg**	**GEn 3600 mg**
Planned, N	98	98

Randomised, N	91	85
Completed, n (%)	79 (87)	82 (96)
Total Number Subjects Withdrawn, n (%)	12 (13)	3 (4)
Withdrawn due to Adverse Events n (%)	3 (3)	0
Withdrawn due to Lack of Efficacy n (%)	4 (4)	0
Withdrawn for other reasons n (%)	5 (5)	3 (4)
Demographics	**Total**	
N (ITT)	93	
Females: Males	36:57	
Mean Age, years (SD)	63.0 (12.15)	
White, n (%)	74 (80)	
Baseline 24 hour Average Pain Intensity, mean (SD)	6.21 (1.476)	
Primary Efficacy Results:		
24-Hour Average Pain Intensity	**GEn 1200 mg**	**GEn 3600 mg**
N (ITT)	90	85
Mean Baseline 24-hour Average Pain Intensity (SD)	6.23 (1.478)	6.14 (1.425)
Change from Baseline at End of Treatment (LOCF) ,n	90	84
Unadjusted Mean Change (SD)	-1.19 (1.596)	-1.50 (1.745)
Adjusted Mean Change (SE)	-1.18 (0.171)	-1.47 (0.173)
Adjusted Treatment Difference: 3600mg vs 1200mg	-0.29	
90% Confidence Interval (CI)	(-0.48, -0.10)	
Adjusted p-value	0.013	
24-Hour Average Pain Intensity by period:	**GEn 1200 mg**	**GEn 3600 mg**
Period 1, N(ITT)	49	44
Baseline, n	49	44
Mean Baseline 24-hour Average Pain Intensity (SD)	6.38 (1.476)	6.03(1.473)
Change from Baseline at End of Treatment Period 1 (LOCF) ,n	49	43
Unadjusted mean change (SD)	-1.11 (1.477)	-1.09 (1.366)
Period 2, N(ITT)	41	41
Baseline, n	41	41
Mean Baseline 24-hour Average Pain Intensity (SD)	6.05 (1.480)	6.25 (1.382)
Change from Baseline at End of Treatment Period 2 (LOCF) ,n	41	41
Unadjusted mean change (SD)	-1.29 (1.742)	-1.92 (2.00)
Secondary Outcome Variable(s) (ITT Population):		
Day-time, Night-time and Current Pain Assessments from e-Diary		
	GEn 1200 mg	**GEn 3600 mg**
N(ITT)	90	85
Day-time average pain		
Baseline, n	90	85
Baseline Mean (SD)	6.17 (1.541)	6.07 (1.496)
Change from Baseline at End of Treatment (LOCF), n	90	84
Unadjusted mean change (SD)	-1.18 (1.608)	-1.49 (1.729)
Adjusted Mean Change (SE)	-1.17 (0.172)	-1.48 (0.174)
Adjusted Mean Difference: 3600mg vs 1200mg	-0.31	
90% Confidence Interval	(-0.51, -0.11)	
Day-time worst pain		
Baseline, n	90	85
Baseline Mean (SD)	6.92 (1.495)	6.85 (1.454)
Change from Baseline at End of Treatment (LOCF), n	90	84
Unadjusted mean change (SD)	-1.18 (1.658)	-1.53 (1.869)
Adjusted Mean Change (SE)	-1.17 (0.178)	-1.50 (0.181)
Adjusted Mean Difference: 3600mg vs 1200mg	-0.33	

90% Confidence Interval	(-0.53, -0.12)	
Current evening pain		
Baseline, n	90	85
Baseline Mean (SD)	6.30 (1.596)	6.21 (1.557)
Change from Baseline at End of Treatment (LOCF), n	90	84
Unadjusted mean change (SD)	-1.10 (1.659)	-1.41 (1.771)
Adjusted Mean Change (SE)	-1.10 (0.180)	-1.39 (0.183)
Adjusted Mean Difference: 3600mg vs 1200mg	-0.29	
90% Confidence Interval	(-0.50, -0.08)	
Night-time average pain		
Baseline, n	90	85
Baseline Mean (SD)	5.54 (2.141)	5.42 (2.10)
Change from Baseline at End of Treatment (LOCF), n	89	85
Unadjusted mean change (SD)	-1.00 (1.776)	-1.24 (2.041)
Adjusted Mean Change (SE)	-0.92 (0.188)	-1.21 (0.190)
Adjusted Mean Difference: 3600mg vs 1200mg	-0.29	
90% Confidence Interval	(-0.54, -0.05)	
Night-time worst pain		
Baseline, n	90	85
Baseline Mean (SD)	6.15 (2.268)	6.06 (2.242)
Change from Baseline at End of Treatment (LOCF), n	89	85
Unadjusted mean change (SD)	-1.06 (1.852)	-1.37 (2.044)
Adjusted Mean Change (SE)	-0.97 (0.192)	-1.33 (0.194)
Adjusted Mean Difference: 3600mg vs 1200mg	-0.36	
90% Confidence Interval	(-0.61, -0.12)	
Current morning pain		
Baseline, n	90	85
Baseline Mean (SD)	6.16 (1.738)	6.08 (1.686)
Change from Baseline at End of Treatment (LOCF), n	89	85
Unadjusted mean change (SD)	-1.16 (1.730)	-1.48 (1.935)
Adjusted Mean Change (SE)	-1.11 (0.187)	-1.46 (0.189)
Adjusted Mean Difference: 3600mg vs 1200mg	-0.35	
90% Confidence Interval	(-0.59, -0.11)	
Responder Rates for 24-Hour Average Pain Intensity		
Percentage Reduction from Baseline to End of Treatment (LOCF)	**GEn 1200 mg n(%)**	**GEn 3600 mg n(%)**
N(ITT)	90	85
n	90	84
≥0	68 (76)	71 (85)
≥10	51 (57)	49 (58)
≥20	39 (43)	42 (50)
≥30%	28 (31)	32 (38)
≥40	17 (19)	26 (31)
≥50%	15 (17)	16 (19)
≥60	6 (7)	11 (13)
≥70%	4 (4)	5 (6)
≥80	1 (1)	2 (2)
≥90	1 (1)	2 (2)
=100%	0	2 (2)
Responder Rates for 24-Hour Average Pain Intensity by Period		
Percentage Reduction from Baseline to End of Treatment (LOCF)	**GEn 1200 mg n(%)**	**GEn 3600 mg n(%)**
Period 1, N(ITT)	49	44

n	49	43
≥0	38 (78)	34 (79)
≥10	26 (53)	23 (53)
≥20	19 (39)	19 (44)
≥30%	13 (27)	13 (30)
≥40	9 (18)	10 (23)
≥50%	7 (14)	5 (12)
≥60	1 (2)	3 (7)
≥70%	0	0
≥80	0	0
≥90	0	0
=100%	0	0
Period 2, N (ITT)	41	41
n	41	41
≥0	30 (73)	37 (90)
≥10	25 (61)	26 (63)
≥20	20 (49)	23 (56)
≥30%	15 (37)	19 (46)
≥40	8 (20)	16 (39)
≥50%	8 (20)	11 (27)
≥60	5 (12)	8 (20)
≥70%	4 (10)	5 (12)
≥80	1 (2)	2 (5)
≥90	1 (2)	2 (5)
=100%	0	2 (5)
Global Impression of Change at End of Treatment (LOCF)		
	GEn 1200 mg	**GEn 3600 mg**
N(ITT)	90	85
Patient Global Impression of Change (PGIC)		
n	63	61
PGIC Responders, n (%)	17 (27)	28 (46)
Clinician Global Impression of Change (CGIC)		
n	53	48
CGIC Responders n (%)	15 (28)	18 (38)
Global Impression of Change at End of Treatment by Period (LOCF)		
Period 1, N(ITT)	49	44
PGIC at End of Treatment Period 1, n	35	27
PGIC Responders n (%)	6 (17)	11 (41)
CGIC at End of Treatment Period 1, n	28	22
CGIC Responders n (%)	5 (18)	8 (36)
Period 2, N(ITT)	41	41
PGIC at End of Treatment Period 2, n	28	34
PGIC Responders n (%)	11 (39)	17 (50)
CGIC at End of Treatment Period 2, n	25	26
CGIC Responders n (%)	10 (40)	10 (38)
Daily Dosage of Recue Medication (mg)		
	GEn 1200 mg	**GEn 3600 mg**
Baseline, n	90	85
Baseline Mean (SD)	706.2 (892.75)	663.2 (857.81)

Change from Baseline to End of Treatment (LOCF), n	90	84
Unadjusted mean change (SD)	-79.2 (756.20)	-60.4 (800.27)
Adjusted Mean Change (SE)	-68.18 (73.404)	-71.26 (74.746)
Adjusted Mean Difference: 3600mg vs 1200mg	-3.08	
90% Confidence Interval	-105.02, 98.86	
Sleep Interference score (11-pt NRS)		
	GEn 1200 mg	**GEn 3600 mg**
Baseline, n	90	85
Baseline Mean (SD)	4.81 (2.575)	4.72 (2.579)
Change from Baseline at End of Treatment (LOCF), n	89	85
Unadjusted mean change (SD)	-1.05 (2.165)	-1.25 (2.128)
Adjusted Mean Change (SE)	-0.97 (0.205)	-1.23 (0.207)
Adjusted Mean Difference: 3600mg vs 1200mg	-0.27	
90% Confidence Interval	(-0.52, -0.02)	
Summary of Brief Pain Inventory Severity and Interference of Pain Score		
Brief Pain Inventory Severity of Pain	**GEn 1200 mg**	**GEn 3600 mg**
Baseline, n	78	73
Baseline Mean (SD)	6.21 (1.663)	6.10 (1.602)
Change from Baseline at End of Treatment (LOCF), n	62	60
Unadjusted mean change (SD)	-1.20 (1.755)	-1.68 (1.901)
Adjusted Mean Change (SE)	-1.17 (0.223)	-1.63 (0.225)
Adjusted Mean Difference: 3600mg vs 1200mg	-0.46	
90% Confidence Interval	(-0.84, -0.08)	
Brief Pain Inventory Interference of Pain	**GEn 1200 mg**	**GEn 3600 mg**
Baseline, n	78	73
Baseline Mean (SD)	4.38 (2.481)	4.20 (2.430)
Change from Baseline at End of Treatment (LOCF), n	62	60
Unadjusted mean change (SD)	-0.91 (2.137)	-1.55 (2.297)
Adjusted Mean Change (SE)	-0.82 (0.244)	-1.57 (0.247)
Adjusted Mean Difference: 3600mg vs 1200mg	-0.76	
90% Confidence Interval	(-1.19, -0.32)	

Summary of Estimated Gabapentin Exposures at Steady State
PK Analysis Population (N=82)

Parameters	GEn Regimens	Geo mean	Coefficient of Variation	Median	[5th-95th%]
$AUC_{0-24,ss}$ μg*h/mL	1200 mg 3600 mg	99.2 296.7	32% 34%	99.1 291.9	[70-177.9] [204.6-534.2]
Cave,ss μg/mL	1200 mg 3600 mg	4.1 12.4	32% 34%	4.1 12.2	[2.9-7.4] [8.5-22.2]
Peak-Trough ratio	1200 mg 3600 mg	1.64 1.64	40% 40%	1.5 1.5	[1.2-2.9] [1.2-3]
Cmin μg/mL	1200 mg 3600 mg	3.0 9.2	43% 45%	3.0 8.9	[1.7-6.1] [4.5-18.5]
Cmax μg/mL	1200 mg 3600 mg	5.1 15.2	34% 35%	5.1 15.0	[3.4-9] [9.9-27]

Safety Results: On-therapy

A treatment emergent AE (TEAE) was defined as an AE with onset on or after the start date of investigational product (including Treatment Period 1, Crossover, Treatment Period 2 and Down-titration) but not later than one day after last date of investigational product. TEAEs that were incurred during Baseline Period (GBP1800mg) among the subjects who were part of safety population were also assessed and presented.

	Baseline GBP 1800	GEn 1200 mg	Crossover GEn 2400 mg	GEn 3600 mg	Down-Titration	GEn (Total)
N(Safety)	**94**	91	82	85	80	94
Most Frequent Adverse Events – On-Therapy (At least 5 most frequently reported AEs per treatment group)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with any AE(s), n (%)	4 (4)	27 (30)	5 (6)	21 (25)	7 (9)	42 (45)
Nasopharyngitis	0	4 (4)	0	1 (1)	0	5 (5)
Dizziness	0	0	1 (1)	3 (4)	0	4 (4)
Headache	1 (1)	1 (1)	0	3 (4)	0	4 (4)
Nausea	0	3 (3)	0	0	1 (1)	4 (4)
Fatigue	0	0	1 (1)	2 (2)	0	3 (3)
Post herpetic neuralgia	0	3 (3)	0	0	0	3 (3)
Somnolence	0	1 (1)	0	2 (2)	0	3 (3)
Constipation	0	2 (2)	0	0	0	2 (2)
Diabetes mellitus	0	0	1 (1)	1 (1)	0	2 (2)
Dyspepsia	0	0	0	2 (2)	0	2 (2)
Irritability	0	2 (2)	0	0	0	2 (2)
Nephrolithiasis	0	0	0	2 (2)	0	2 (2)
Rash pruritic	0	2 (2)	0	0	0	2 (2)
Oedema peripheral	1 (1)	1 (1)	0	1 (1)	0	2 (2)
Myalgia	0	0	0	1 (1)	1 (1)	2 (2)
Asthenia	0	0	1 (1)	0	0	1 (1)
Feeling Abnormal	0	0	1 (1)	0	0	1 (1)
Alanine aminotransferase increased	0	0	1 (1)	0	1 (1)	1 (1)
Aspartate aminotransferase increased	0	0	1 (1)	0	1 (1)	1 (1)
Carbon dioxide increased	0	0	1 (1)	0	0	1 (1)
Vision blurred	1 (1)	0	0	1 (1)	0	1 (1)
Colitis ulcerative	0	0	0	0	1 (1)	1 (1)
Migraine	0	0	0	0	1 (1)	1 (1)
Gastroenteritis viral	0	0	0	0	1 (1)	1 (1)
Hallucination auditory	0	0	0	0	1 (1)	1 (1)
Diarrhoea	1 (1)	0	0	0	0	0
Dry mouth	1 (1)	0	0	0	0	0
Hyperaesthesia	1 (1)	0	0	0	0	0
Cystitis	1 (1)	0	0	0	0	0
Libido increased	1 (1)	0	0	0	0	0

Serious Adverse Events – On-Therapy n (%) [n considered by the investigator to be related to study medication]
Serious Adverse events (SAEs) beginning during treatment but no later than one day after the last dose of investigational product (including titration, maintenance and taper phases) were considered treatment-emergent. Subjects with any SAEs includes both fatal and non-fatal events.

	Baseline GBP 1800	GEn 1200 mg	Crossover GEn 2400 mg	GEn 3600 mg	Down-Titration	GEn (Total)
N(Safety)	**94**	**91**	**82**	**85**	**80**	**94**
Subjects with non-fatal SAEs, n (%)	0	0	0	0	1(1)	1(1)
	n (%) [related]	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**
Hallucination, auditory	0	0	0	0	1 (1) [0]	1(1) [0]
Subjects with fatal SAEs, n (%)	0	0	0	0	0	0

Conclusion: In this double-blind, two-period cross-over study, 3600 mg/day of GSK1838262 demonstrated a statistically significant improvement over 1200 mg/day of GSK1838262 on the primary endpoint, which was the change from baseline to the end of the treatment period in the 24-hour average pain intensity score. A greater reduction in the 24-hour average pain score was observed for the 3600 mg/day dose than for the 1200 mg/day dose (adjusted difference of -0.29; p=0.013). In the absence of a placebo comparator and a washout period between the treatment periods, it is difficult to ascertain with certainty whether the treatment effect observed only in Treatment Period 2 was related to study drug or other factors, including study design. In addition, the observed treatment difference of 0.29 was less than the pre-specified treatment difference of 0.6 that the study was powered to detect. The observed treatment difference of 0.29 was statistically significant due to a smaller than expected standard deviation.
The only treatment-emergent adverse event occurring in greater than or equal to 5% of subjects taking GSK1838262 was nasopharyngitis (5%). Among the other adverse events noted in this study, dizziness and somnolence occurred at rates of 4% and 3%, respectively, and were mild in intensity. Withdrawals due to adverse events during GSK1838262 treatment occurred in 3% of subjects.

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