Peripheral Edema and Weight Gain in Adult Patients With Painful Diabetic Peripheral Neuropathy Receiving Gabapentin Enacarbil or Pregabalin Enrolled in a Randomized, Phase 2 Trial

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Disclosures

- AC is a speaker for Depomed, Pfizer, Purdue, Salix, and Teva
- JS served as a consultant for Millennium, XenoPort, Insys, Purdue Frederick, Teva, Empi/Donjoy, Takeda, RS Medical, Covidien, Mallinckrodt, Reckitt Benckiser, and Neurotech
- MJ is a consultant for XenoPort, Inc
- RK and GS are employees of and own stock in XenoPort, Inc

Disclosures (continued)

- Gabapentin enacarbil is not approved for use in the treatment of Diabetic Peripheral Neuropathy (DPN)

- Gabapentin enacarbil is approved for the treatment of adults with moderate-to-severe primary Restless Legs Syndrome (600 mg once daily) and for the management of Postherpetic Neuralgia (PHN; 600 mg twice daily).

Background

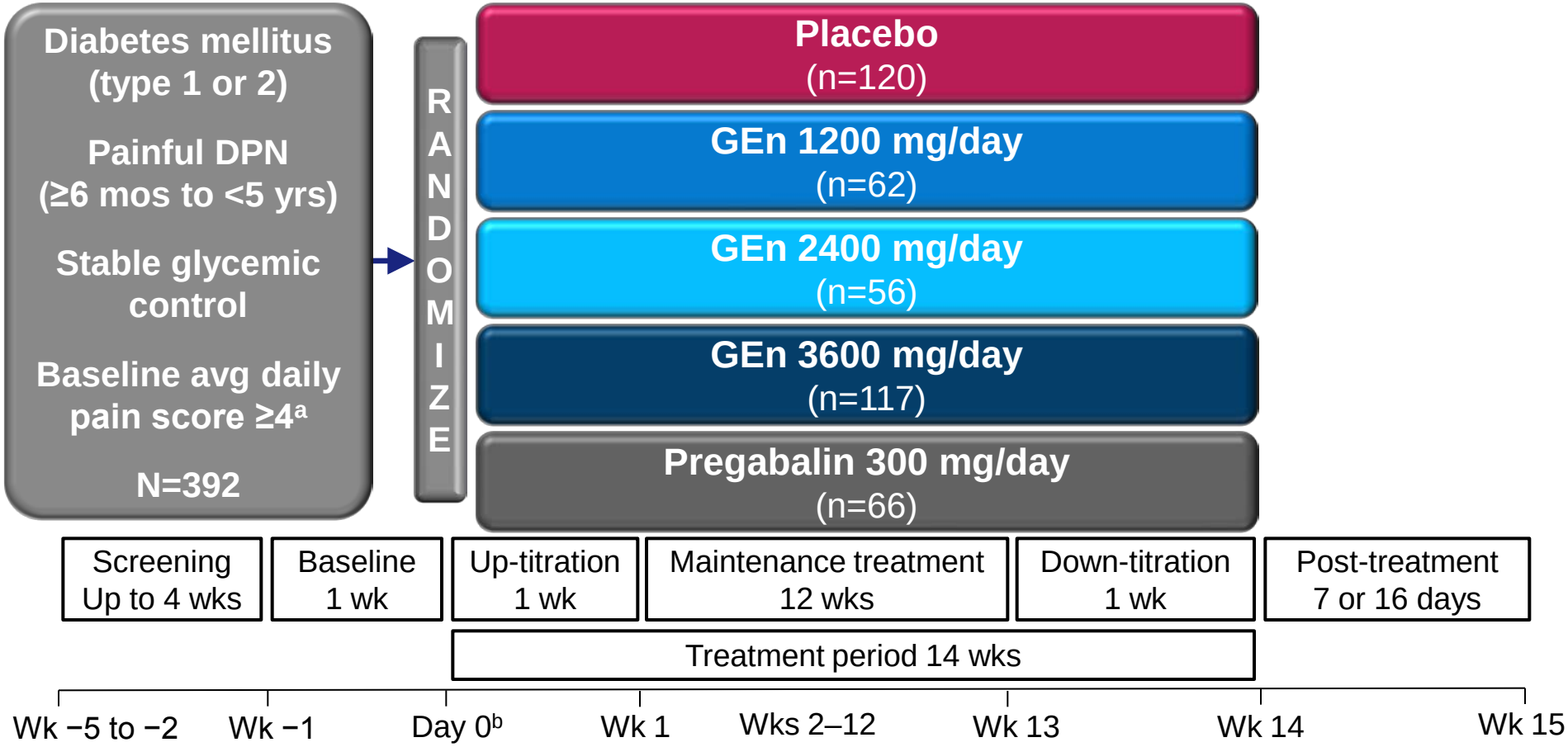
- Gabapentin enacarbil (GEn) is an actively transported prodrug of gabapentin
- GEn was evaluated in a randomized, phase 2 study in patients with neuropathic pain attributed to Diabetic Peripheral Neuropathy (DPN)[1]
- For the primary efficacy endpoint (change from baseline in the mean 24-hour average pain intensity score), neither the GEn treatment arms (1200 mg, 2400 mg, or 3600 mg per day) nor the control arm (pregabalin 300 mg/day) differed from placebo, mostly due to a high placebo response rate
  - Treatment differences vs. placebo: GEn 1200 mg/day: −0.35; P=0.295
    GEn 2400 mg/day: −0.02; P=0.946
    GEn 3600 mg/day: −0.55; P=0.105
    Pregabalin: 0.43; did not differentiate from placebo
- GEn was well tolerated across all studied doses, even at the highest dose of 3600 mg/day[1]

1. Rauck R et al. *Pain Practice* 2013; 13:485-496.

Objective

- As this was the first study to assess treatment with GEn compared with the approved dose of pregabalin, two treatment-emergent adverse events of clinical significance commonly reported with treatment with the alpha-2-delta class of drugs, peripheral edema and weight gain, were further examined

Study Design



[a]On an 11-point pain intensity numerical rating scale (0=no pain; 10=worst possible pain).
[b]Randomization occurred at Day 0.
GEn = gabapentin enacarbil; mos = months; wk = week; yrs = years.
Rauck R et al. *Pain Practice* 2013; 13:485-496.

Baseline Characteristics (Safety Population[a])

Characteristic	Placebo (n=120)	GEn			Pregabalin (n=66)
		1200 mg (n=62)	2400 mg (n=56)	3600 mg (n=116)	
Age, years					
Mean (SD)	60.1 (10.6)	57.5 (10.3)	60.8 (9.0)	57.5 (9.9)	57.7 (10.6)
Gender, %					
Male	61	55	66	61	52
Race, %					
White	82	74	85	79	81
BMI, n (%)					
≤30 kg/m²	27 (23)	16 (26)	22 (39)	39 (34)	17 (26)
>30 kg/m²	93 (78)	46 (74)	34 (61)	77 (66)	49 (74)
Baseline 24-h pain score,					
Mean (SD)	6.5 (1.3)	6.6 (1.5)	6.3 (1.2)	6.5 (1.4)	6.5 (1.3)
HbA1c, %					
Mean (SD)	7.5 (1.3)	7.4 (1.3)	7.6 (1.4)	7.6 (1.4)	7.5 (1.3)

[a]421 patients were randomized to treatment; one patient in the GEn 3600-mg group did not take study medication and was excluded from the safety population.

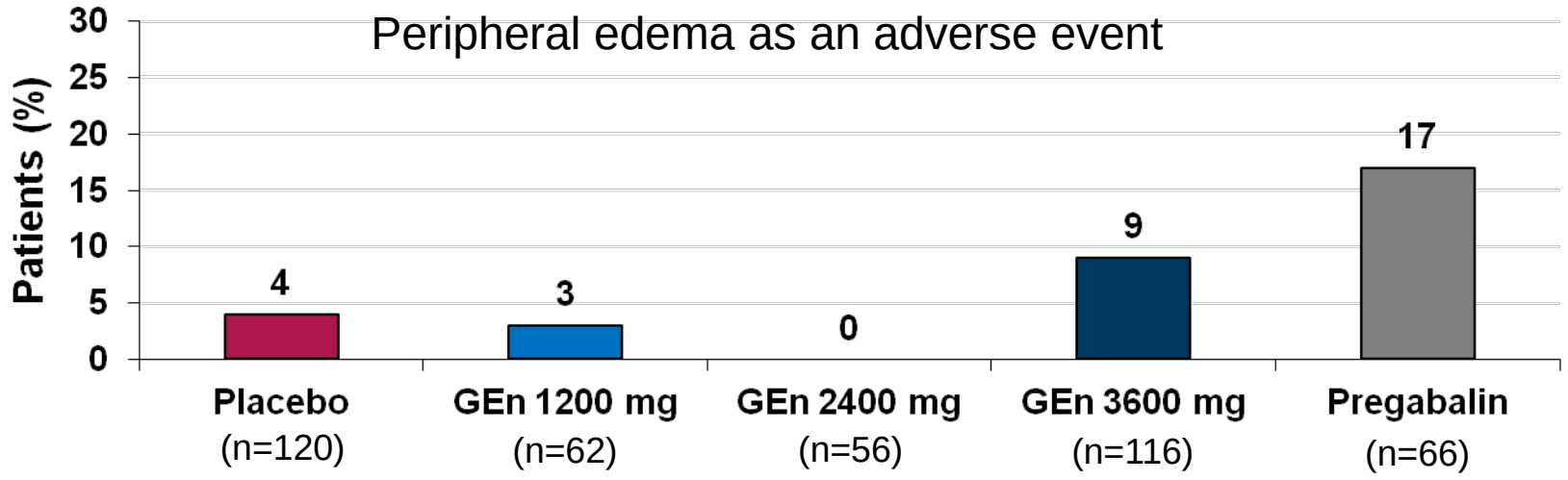
BMI = body mass index; GEn = gabapentin enacarbil; HbA1c = glycated hemoglobin; SD = standard deviation.

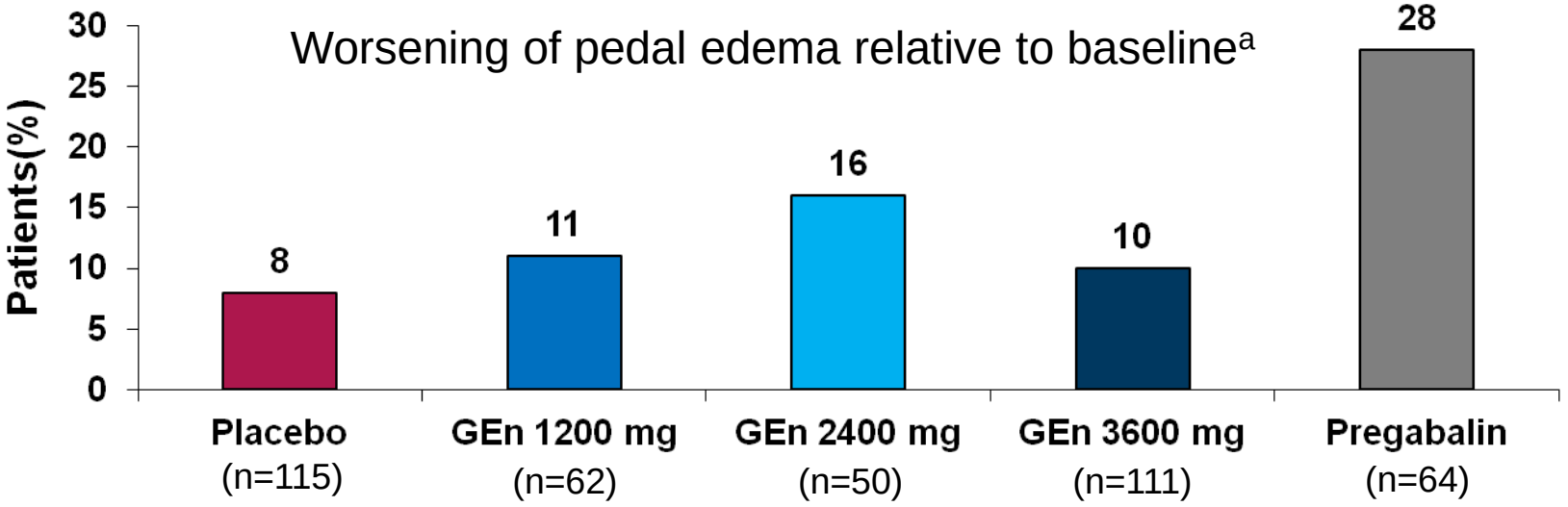
Treatment-Emergent Adverse Events Reported in >5% of Patients (Safety Population)

Adverse event, n (%)	Placebo (n=120)	GEn 1200 mg (n=62)	GEn 2400 mg (n=56)	GEn 3600 mg (n=116)	Pregabalin (n=66)
Any event	79 (66)	45 (73)	38 (68)	86 (74)	47 (71)
Dizziness	7 (6)	9 (15)	8 (14)	16 (14)	9 (14)
Somnolence	5 (4)	2 (3)	7 (13)	14 (12)	9 (14)
Nausea	9 (8)	7 (11)	4 (7)	7 (6)	3 (5)
Peripheral edema	5 (4)	2 (3)	0	11 (9)	11 (17)
Headache	9 (8)	3 (5)	4 (7)	4 (3)	6 (9)
Increased weight	1 (<1)	0	2 (4)	5 (4)	5 (8)
Other treatment-emergent adverse events reported in >5% of patients included muscle spasms, diarrhea, urinary tract infection, constipation, fatigue, dry mouth, and pain in extremity					

GEn = gabapentin enacarbil.

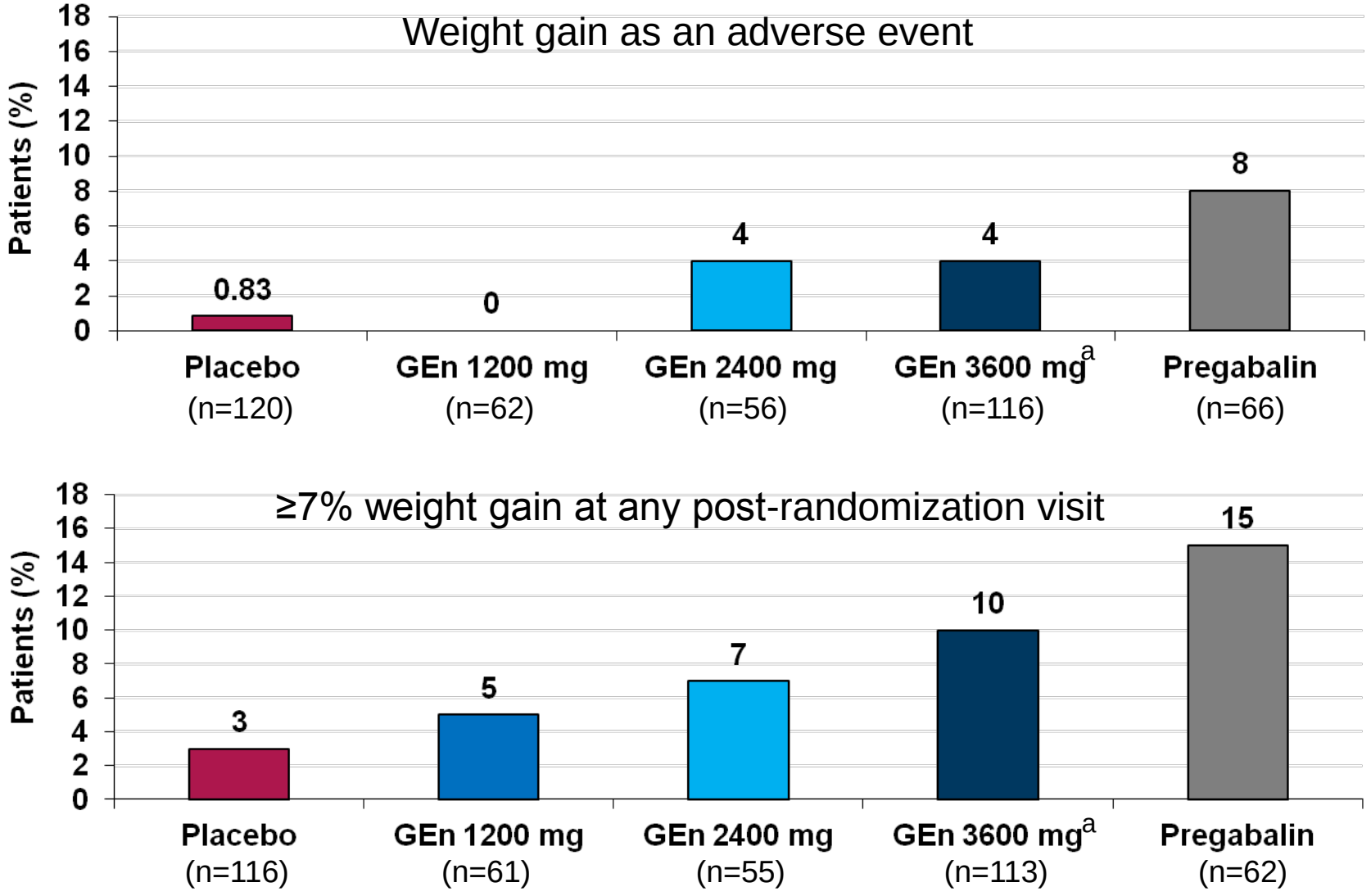
Peripheral and Pedal Edema





[a]Worsening = positive change in grade; GEn = gabapentin enacarbil.

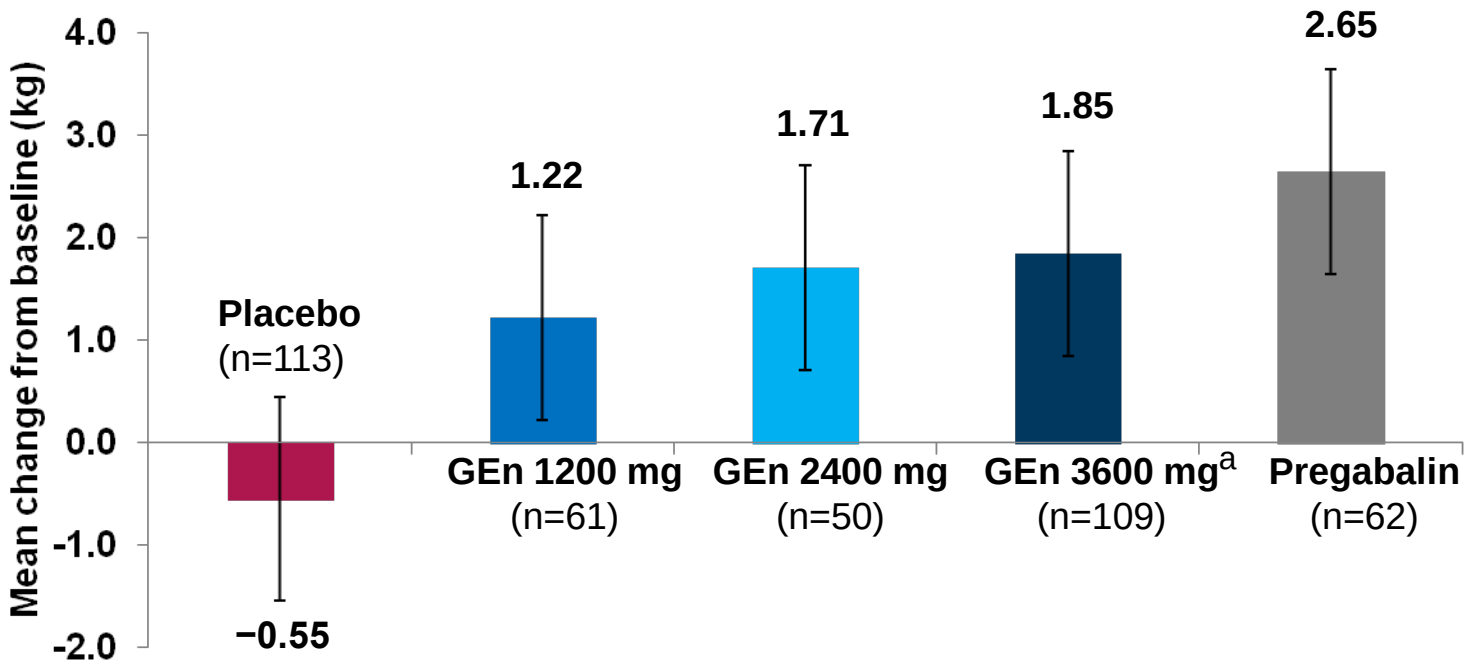
Weight Gain



[a]One subject excluded due to implausible weight change data. GEn = gabapentin enacarbil.

Mean Change From Baseline in Weight Gain at Week 13 or Early Termination (LOCF)

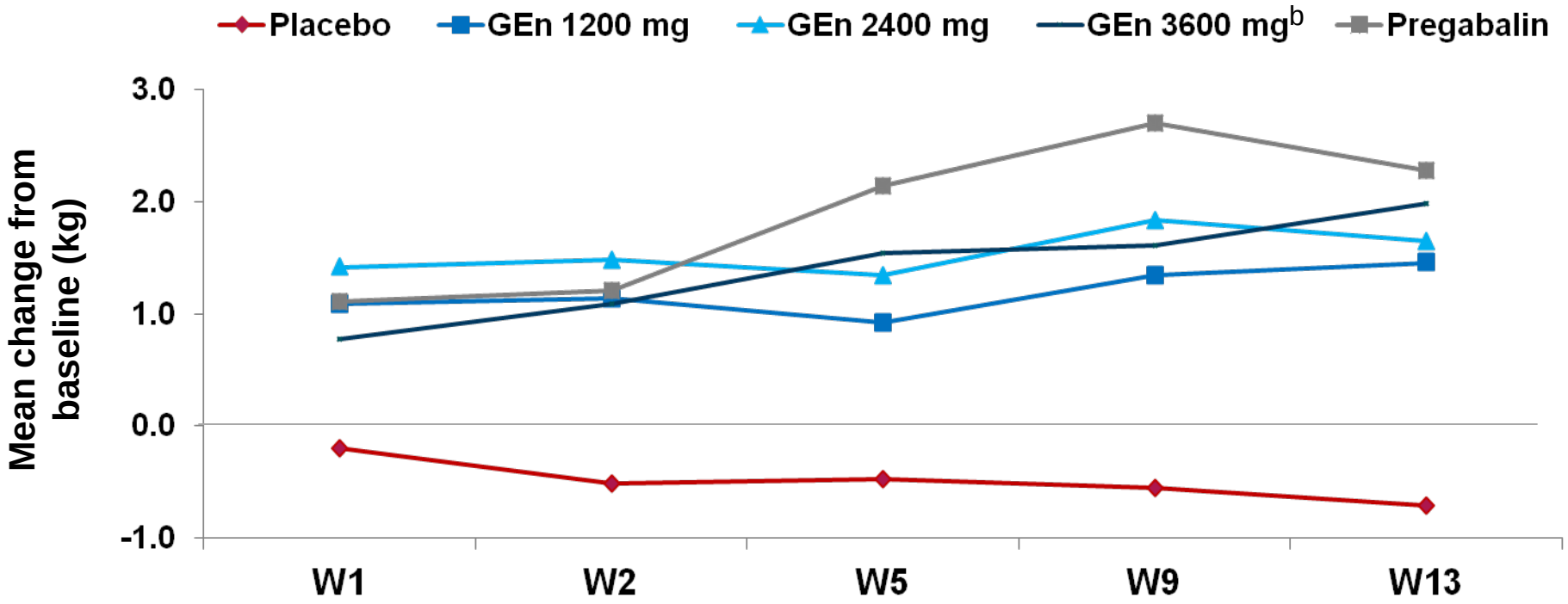
Observed mean (±2 SE) change from baseline in weight gain at week 13/ET (LOCF)



[a]One subject excluded due to implausible weight change data

ET = early termination; LOCF= last observation carried forward; SE = standard error.

Mean Change From Baseline in Weight Gain[a]



Patients, N					
Placebo	112	108	103	97	90
GEn 1200 mg	61	58	57	51	48
GEn 2400 mg	49	48	43	40	39
GEn 3600 mg	109	106	96	84	81
Pregabalin	62	60	55	53	46

[a]Observed data.
[b]One subject excluded due to implausible weight change data.
GEn = gabapentin enacarbil; W = week.

Conclusions

- In this phase 2 study in patients with painful DPN, treatment with GEn was associated with overall lower incidences of peripheral edema and weight gain compared with pregabalin
  - This was most evident with GEn 1200 mg, but even the higher doses of GEn were associated with less weight gain and peripheral edema than pregabalin
  - Weight gain in GEn-treated patients appeared to be dose-dependent
- The observed differences in peripheral edema and weight gain between all GEn doses examined and pregabalin are of clinical significance, given that these treatment-emergent adverse events may lead to limitations in patients' willingness to tolerate and adhere to prescribed regimens
- GEn is approved for the management of PHN in adults at a daily dose of 1200 mg. Additional benefit of using doses greater than 1200 mg/day was not demonstrated, and these higher doses resulted in an increase in adverse reactions

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Backup slides

Patient Disposition

	Placebo	GEn 1200 mg	GEn 2400 mg	GEn 3600 mg	Pregabalin	Total
Randomized, n (%)	120	62	56	117	66	421
Completion status, n (%)						
Completed	90 (75)	47 (76)	37 (66)	79 (68)	47 (71)	300 (71)
Withdrawn	30 (25)	15 (24)	19 (34)	38 (32)	19 (29)	121 (29)
Primary reason for withdrawal, n (%)						
Adverse event	11 (9)	5 (8)	12 (21)	21 (18)	6 (9)	55 (13)
Lack of efficacy	3 (3)	1 (2)	0	4 (3)	3 (5)	11 (3)
Protocol deviation	7 (6)	6 (10)	4 (7)	4 (3)	6 (9)	27 (6)
Lost to follow-up	6 (5)	2 (3)	1 (2)	3 (3)	3 (5)	15 (4)
Investigator discretion	0	0	0	2 (2)	0	2 (<1)
Withdrew consent	3 (3)	1 (2)	2 (4)	4 (3)	1 (2)	11 (3)

GEn = gabapentin enacarbil.

Adverse Events Leading to Withdrawal

55 patients withdrew from the study due to AE

List of Preferred Terms for AEs Leading to Withdrawal from the Study (number of days since 1st dose)				
Placebo (N=120)	**GEn 1200mg (N=62)**	**GEn 2400mg (N=56)**	**GEn 3600mg (N=117)**	**Pregabalin (N=66)**
W/D due to AE: 11 (9%)	**W/D due to AE : 5 (8%)**	**W/D due to AE : 12 (21%)**	**W/D due to AE : 21 (18%)**	**W/D due to AE : 6 (9%)**
•Abdominal discomfort (27) •Asthenia (2) •Balance disorder (2) •Chronic lymphocytic leukaemia (35) •Constipation (2) •Diarrhoea (3) •Dizziness (2, 57) •Fatigue (10) •Gastroenteritis viral (30) •Lymphocyte count incr. (1) •Muscle spasms (3) •Nausea (2) •Sinus tachycardia (66) •Somnolence (1) •Supraventricular tachycardia (43) •Vision blurred (2) •Vomiting (3) •WBC count incr. (1)	•Blood creatinine incr. (20) •Blood potassium incr. (20) •Blood urea incr. (20) •Cellulitis (77) •Confusional state (78) •Cough (6) •Lethargy (14) •Memory impairment (14) •Nausea (18) •Skin ulcer (77)	•Abdominal pain (5, 13) •Ankle fracture (72) •Arthralgia (3) •Balance disorder (9) •Bipolar disorder (4) •Confusional state (9) •Constipation (4) •Dizziness (4) •Dry mouth (6) •Headache (9) •Hypoaesthesia (78) •Increased appetite (3) •Lethargy (17) •Partial seizures (6) •Somnolence (2) •Stress fracture (16) •Toothache (55) •Vision blurred (4, 6)	•Affective disorder (5) •Agitation (1) •Ataxia (12) •Back pain (4) •Blood glucose incr. (40) •Constipation (unk., 5) •Coronary artery stenosis (64) •Dizziness (1, 2, 15, 50) •Eye irritation (50) •Headache (1, 57) •HbA1c incr. (61) •Iron deficiency anaemia (57) •Middle insomnia (1) •Muscle spasms (17) •Nausea (1, 50) •Oedema (22) •Oedema peripheral (15, 22) •Pain in extremity (17) •Somnolence (1, 1, 3, 7) •Suicidal ideation (51) •Swelling (7) •Tremor (1) •Vertigo (3) •Vision blurred (1)	•Affective disorder (16) •Amnesia (21) •Constipation (1, 8) •Dizziness (2) •Dyspnoea (21) •Fatigue (2, 34) •Oedema peripheral (66) •Somnolence (2) •Weight increased (77)

Table 3.13 – not formally QC'd; Note: Patients may have reported more than one AE that led to withdrawal from the study.