

# POSITIVE EFFICACY DATA FROM A PHASE 2 TRIAL OF GABAPENTIN EXTENDED-RELEASE IN THE TREATMENT OF MENOPAUSAL HOT FLASHES

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## Background

Gabapentin, given TID, at doses of 900-2400 mg/day has been reported to be effective for the treatment of hot flashes in postmenopausal women.

The absorption of gabapentin is dose-dependent; as the dose is increased, the bioavailability decreases, resulting in a less than proportional increase in gabapentin exposure with dose. This is attributed to a nonlinear absorption due to a saturable uptake of the drug, which accounts for most of its mode of absorption.

A gabapentin extended-release formulation (gER) intended for once-daily or twice-daily administration has been developed using the AcuForm™ technology. AcuForm™ is a polymer-based drug delivery technology which retains the tablet in the stomach and the upper GI tract for a sustained period of time. When administered with a meal, the tablet gradually expands and is retained in the stomach, while releasing the drug via a polymer matrix over an extended period of time to the upper GI tract. The rate of drug release is controlled by the polymer-based technology. This extended release formulation of gabapentin may help to overcome the saturable absorption and to provide a reduced C<sub>max</sub>, more consistent blood levels of drug, and a potential for improved efficacy, tolerability, and patient compliance while minimizing the incidence of adverse events.

## Objective

To determine the safety and efficacy of gabapentin extended-release (gER) for the treatment of vasomotor symptoms in menopause.

## Methods

A Phase 2, randomized, double-blind study was conducted in 124 post-menopausal women who had experienced ≥ 7 moderate to severe hot flashes/day plus sweating during the previous 30 days or longer. Electronic diaries were used to record the occurrence and severity of hot flashes. Intensive PK samplings were conducted over a 24-h period 3 times during the study.

### Key Inclusion Criteria:

- Amenorrhea for at least 12 months; or amenorrhea for 6-12 months with FSH > 40 mIU/mL; or ≥ 6 weeks post surgical bilateral oophorectomy ± hysterectomy

### Randomized Treatment:

- gER 1200 mg AM, 1800 mg PM
- gER 600 mg AM, 1800 mg PM
- gER 600 mg AM, 1200 mg PM
- Placebo

### Dosing Schedule (see Table 1):

- 2 x 6-week periods of active treatment
- 1-week dose tapering

### Primary Efficacy Outcome:

- Mean change in average daily frequency of moderate to severe hot flashes (MSHF) from baseline to endpoint

### Secondary Outcomes:

- Proportion of responders (patients with at least a 75% reduction in average daily frequency of MSHF)
- Percent change from baseline to endpoint in average daily frequency of MSHF
- Clinician global impression of change (CGIC)
- Patient global impression of change (PCIG)
- Incidence of adverse events

## Results

Table 2: Baseline Patient Characteristics

	gER 1800 mg [600/1200] (N = 31)	gER 2400 mg [600/1800] (N = 31)	gER 3000 mg [1200/1800] (n = 32)	Placebo (N = 29)
Age: mean (SD)	54 (6.9)	56 (6.3)	57 (7.2)	56 (5.5)
Race: N %				
White	23 (74.2%)	17 (54.8%)	23 (71.9%)	23 (79.3%)
Other	8 (25.8%)	14 (45.2%)	9 (28.1%)	6 (20.7%)
eC <sub>cr</sub> (mL/Min) Mean (SD)	105 (40)	95 (25)	95 (21)	99 (25)
BMI (Kg/m <sup>2</sup> ) Mean (SD)	29.5 (6.2)	28.3 (5.0)	26.6 (4.9)	28.6 (5.5)
Average daily frequency MSHF: Mean (SD)	9.9 (2.2)	11.6 (4.6)	11.3 (3.5)	10.5 (3.6)
Average daily severity score* MSHF Mean (SD)	2.34 (0.24)	2.50 (0.25)	2.41 (0.28)	2.49 (0.26)

\*Average daily severity score = [(number of moderate hot flashes x 2) + (number of severe hot flashes x 3)]/total daily number of moderate to severe hot flashes

Figure 1: Average Daily Frequency of MSHF by Week

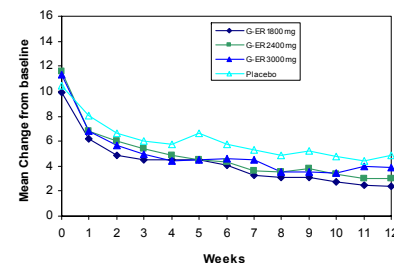
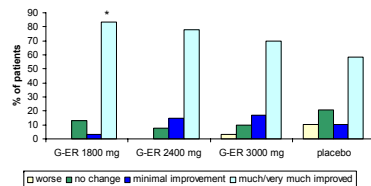
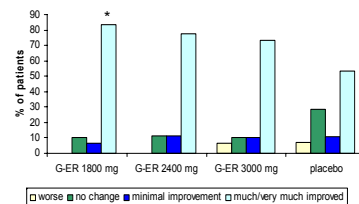


Figure 2: Patient Global Impression of Change at Endpoint



\*p < 0.05 vs. placebo for change from baseline

Figure 3: Clinical Global Impression of Change at Endpoint



\*p < 0.05 vs. placebo for change from baseline

Table 4: Adverse Events

	gER 1800 mg	gER 2400 mg	gER 3000 mg	Placebo
Overall incidence	61.3%	80.6%	71.9%	55.2%
Headache	32.3%	32.3%	25.0%	10.3%
Somnolence	16.1%	16.1%	15.6%	3.4%
Dizziness	9.7%	38.7%	9.4%	10.3%
Leading to withdrawal	headache jitteriness	dizziness	weight gain dizziness	dizziness

- Seven patients discontinued study drug during the treatment period due to an adverse event.
- No treatment-related serious adverse event and no death were reported during the study.

## Conclusions

- Treatments with daily divided doses of gER 1800 mg and gER 2400 mg provided clinically and statistically significant reduction in average daily frequency of MSHF in postmenopausal women compared to placebo.
- Significantly more patients were qualified as responders (achieved a 75% or greater decrease in average daily frequency of MSHF) in the gER 1800 mg treatment group than in the placebo group.
- Patients in the gER 1800 mg treatment group achieved a significant mean reduction in average daily frequency of MSHF of 73% compared to 54% in the placebo group.
- Significantly more patients in the gER 1800 mg treatment group rated themselves as much or very much improved on the PCIG compared to the placebo group.
- Significantly more patients in the gER 1800 mg treatment group rated themselves as much or very much improved on the CCIG compared to the placebo group.
- The types of adverse events observed with gER were similar to those seen in other clinical trials of gabapentin in Hot Flash.
- This clinical study had low withdrawal rate (5.6%), high tolerability, and no evidence of increased efficacy above 1800 mg/day.

Table 1: Titration Schedule

gER	Titration 1 (Week 1)	Weeks 2 - 6	Titration 2 (Week 7)	Weeks 8 - 12
1800 mg N = 31	↑ 600 mg	600 mg PM	↑ 1800 mg	600 mg AM 1200 mg PM
2400 mg N = 30	↑ 1200 mg	600 mg AM 600 mg PM	↑ 2400 mg	600 mg AM 1800 mg PM
3000 mg N = 32	↑ 1200 mg	1200 mg PM	↑ 3000 mg	1200 mg AM 1800 mg PM
Placebo N = 31	Placebo	Placebo	Placebo	Placebo

Table 3: Hot Flashes Interference Scores

MSHF	gER 1800 mg (N = 31)	gER 2400 mg (N = 31)	gER 3000 mg (N = 32)	Placebo (N = 29)
Reduction in average daily frequency LS Mean (SEM)	-8.1 (0.7)*	-7.9 (0.7)*	-6.9 (0.7)	-5.7 (0.7)
% reduction	-73%*	-70%	-63%	-54%
% responders†	63%*	50%	56%	37%

\*P < 0.05 vs. placebo

† patients with 75% or greater reduction in average daily MSHF from baseline to endpoint