



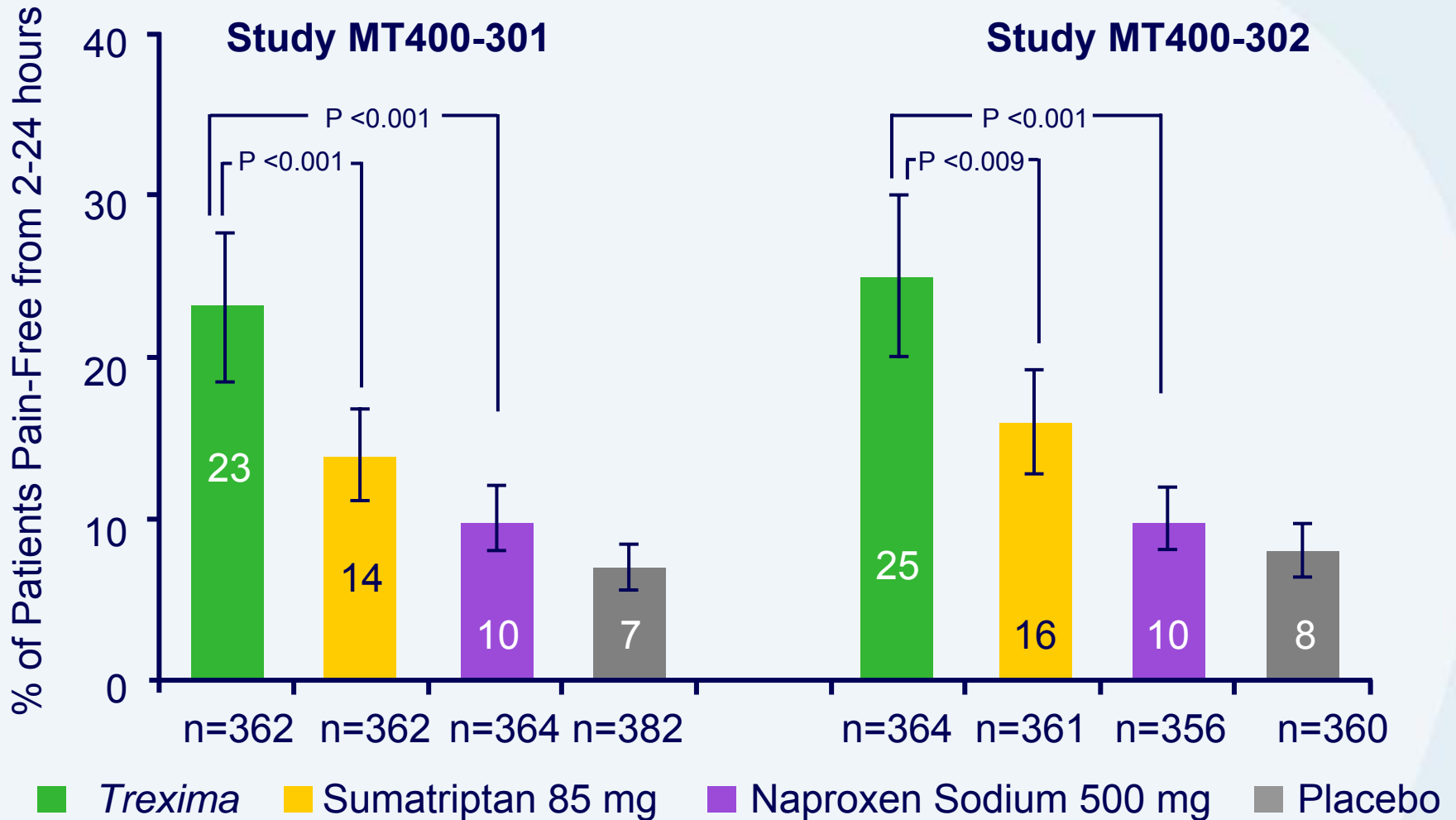
GSK Neurosciences: Late-Stage Portfolio

Atul Pande

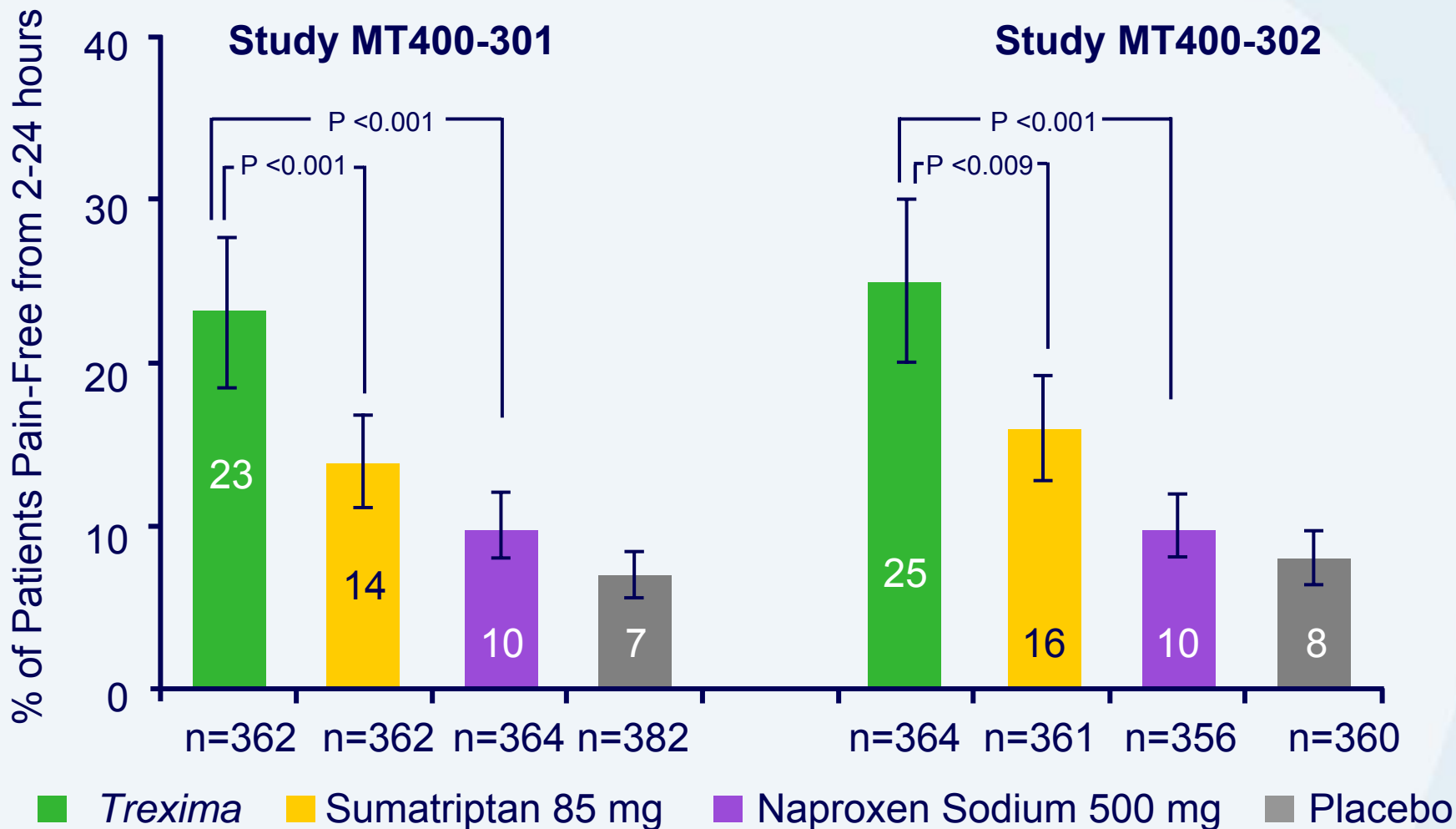
Late-stage pipeline

- *Trexima**

Potential new gold standard migraine treatment



Potential new gold standard migraine treatment



PDUFA date: 15 April 2008

Late-stage pipeline

- *Trexima*

- *Requip XL** for Parkinson's

- First oral once-a-day dopamine agonist
- Approved in EU, and approvable in the US (Dec. 7th)

Late-stage pipeline

- *Trexima*
- *Requip XL* for Parkinson's
- *Lunivia** in Europe – filed in July

Late-stage pipeline

- *Trexima*
- *Requip XL* for Parkinson's
- *Lunivia* in Europe – filed in July
- *Lamictal XR* for epilepsy: “approvable” Sept. '07

Late-stage pipeline

- *Trexima*
- *Requip XL* for Parkinson's
- *Lunivia* in Europe – filed in July
- *Lamictal XR* for epilepsy: “approvable” Sept. '07
- rosiglitazone XR in Alzheimer's disease

Late-stage pipeline

- *Trexima*
- *Requip XL* for Parkinson's
- *Lunivia* in Europe – filed in July
- *Lamictal XR* for epilepsy: “approvable” Sept. '07
- rosiglitazone XR in Alzheimer's disease
- GSK 1838262 (XP13512*)

GSK '262

```
graph TD; GSK('GSK '262') --- RLS('Restless Legs Syndrome (RLS)'); GSK --- MP('Migraine Prophylaxis'); GSK --- NP('Neuropathic Pain'); GSK --- MD('Mechanism for Differentiation');
```

**Restless Legs Syndrome
(RLS)**

Migraine Prophylaxis

Neuropathic Pain

**Mechanism for
Differentiation**

Limitations of gabapentin

Suboptimal Efficacy

- **70% Partial / Non-Responders** in Post-Herpetic Neuralgia Trials
- Not approved for any other pain indications (US)

Limitations of gabapentin

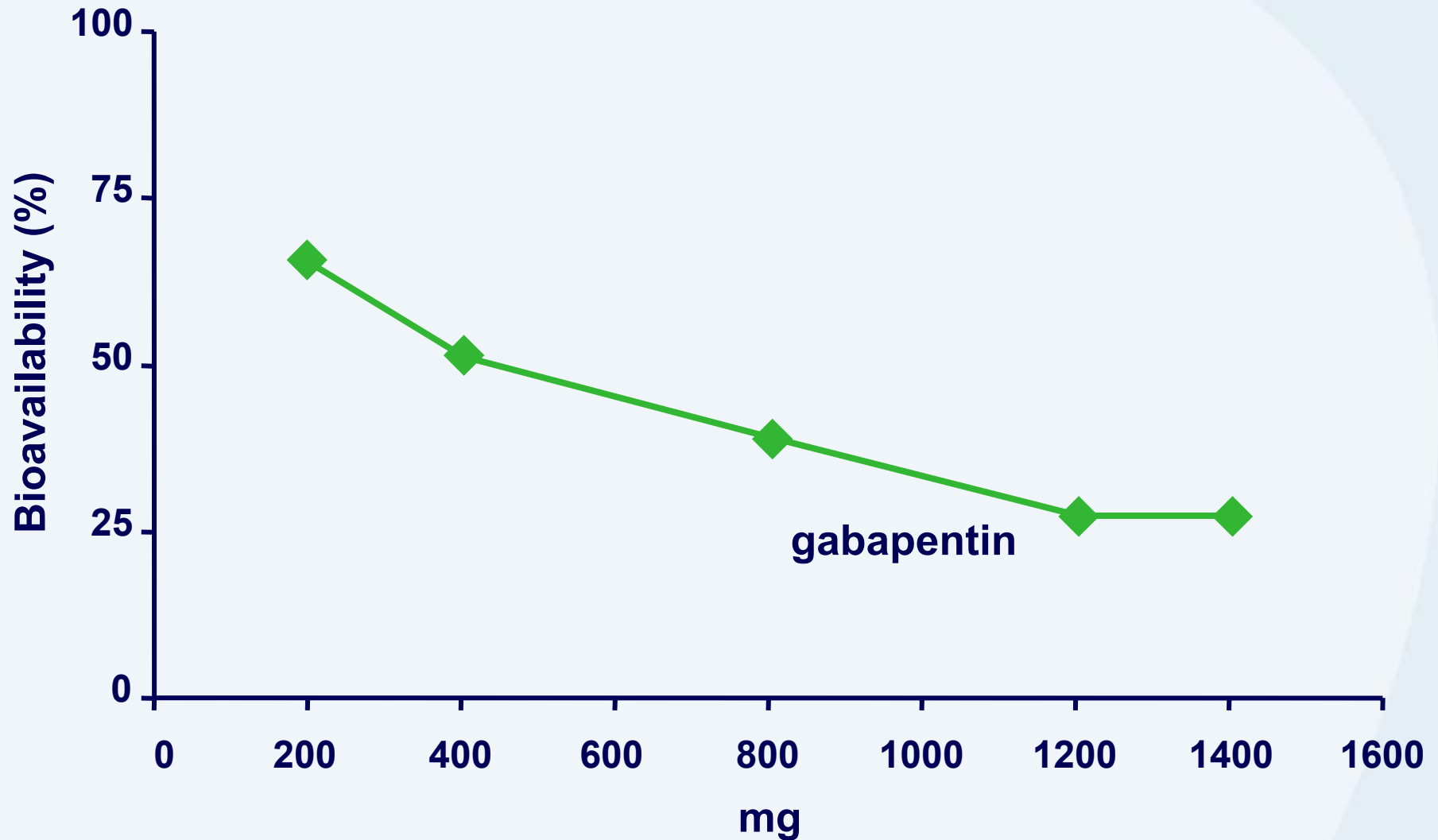
Suboptimal Efficacy

- **70% Partial / Non-Responders** in Post-Herpetic Neuralgia Trials
- Not approved for any other pain indications (US)

Suboptimal Pharmacokinetics

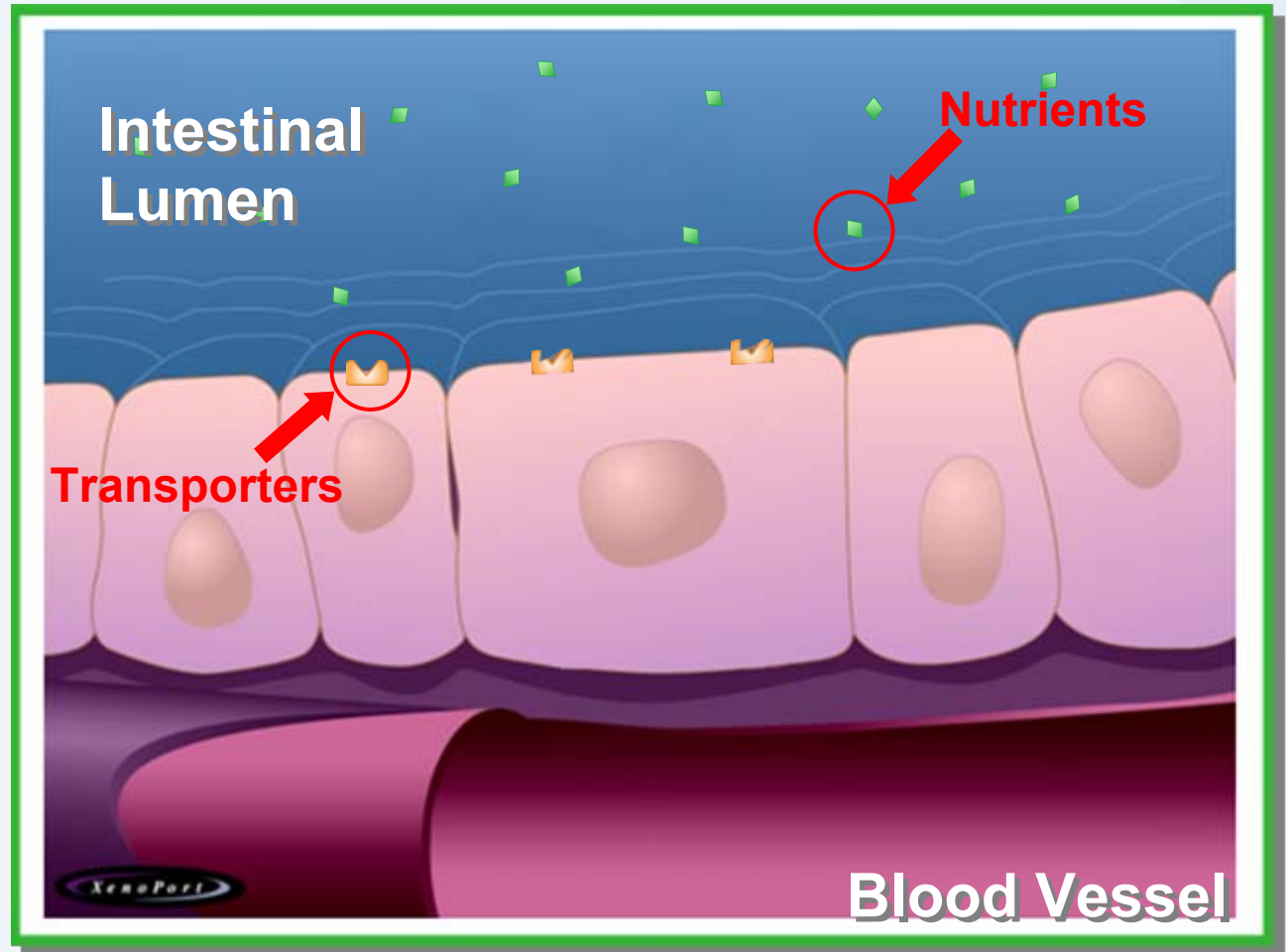
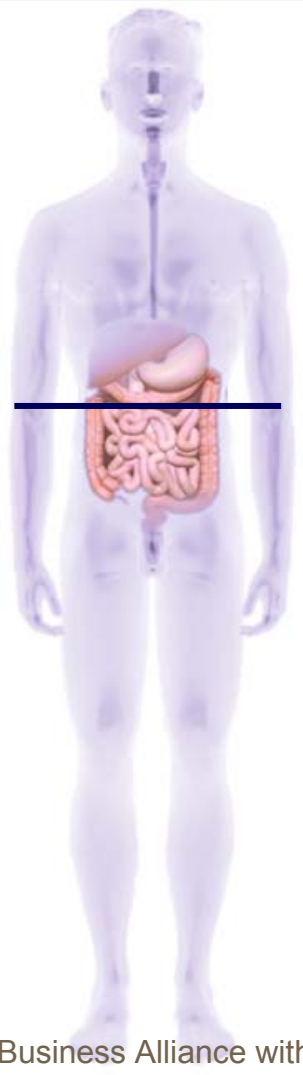
- High Inter-Patient Variability
- Ceiling on Attainable Blood Levels
- Short Half-Life Requires Dosing Three Times a Day
- No Sustained Release Formulation

Absorption of gabapentin decreases with increasing dose

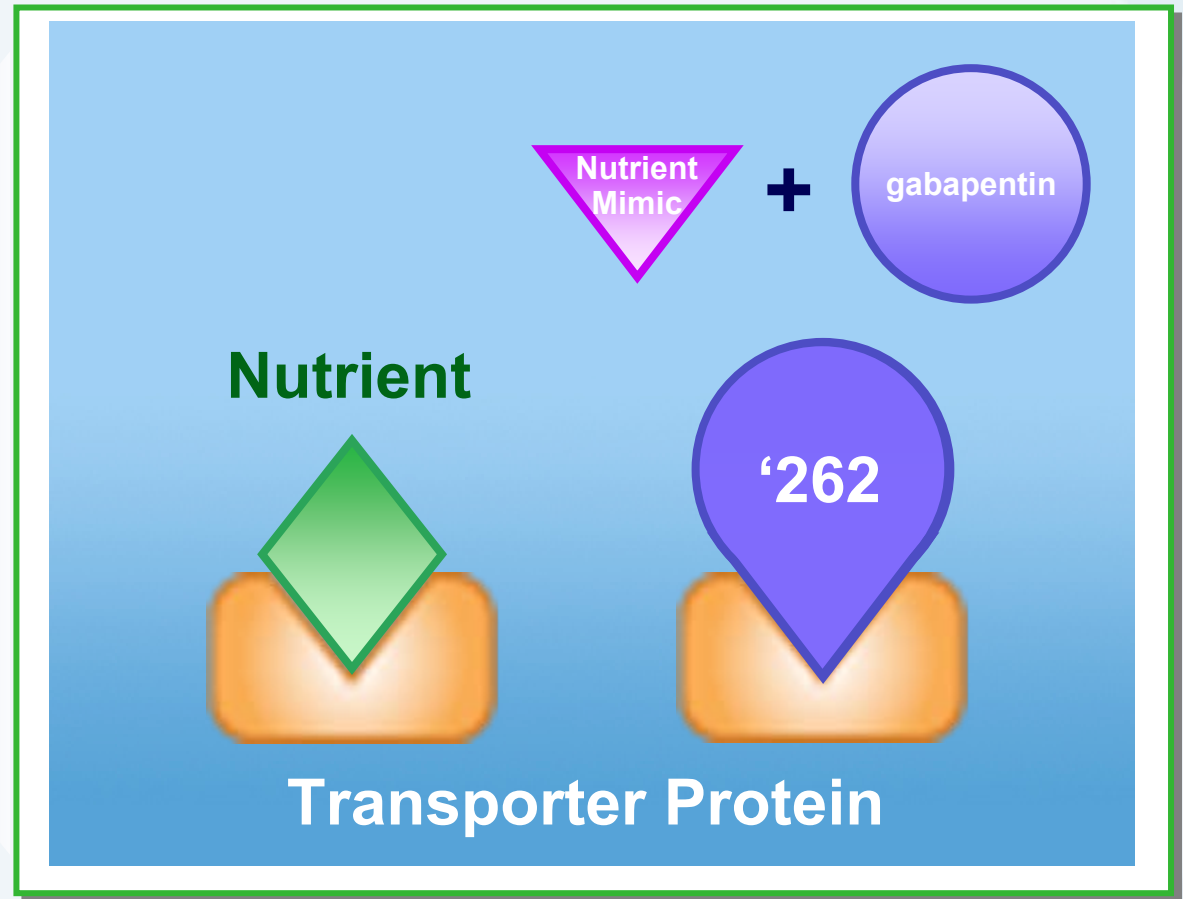


Intestinal absorption of orally given drugs

Nutrients Absorbed Through Active Transport



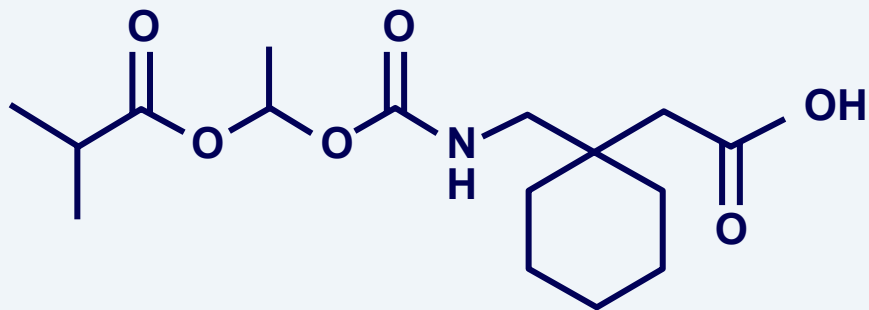
Design of GSK '262



GSK '262 chemical structure



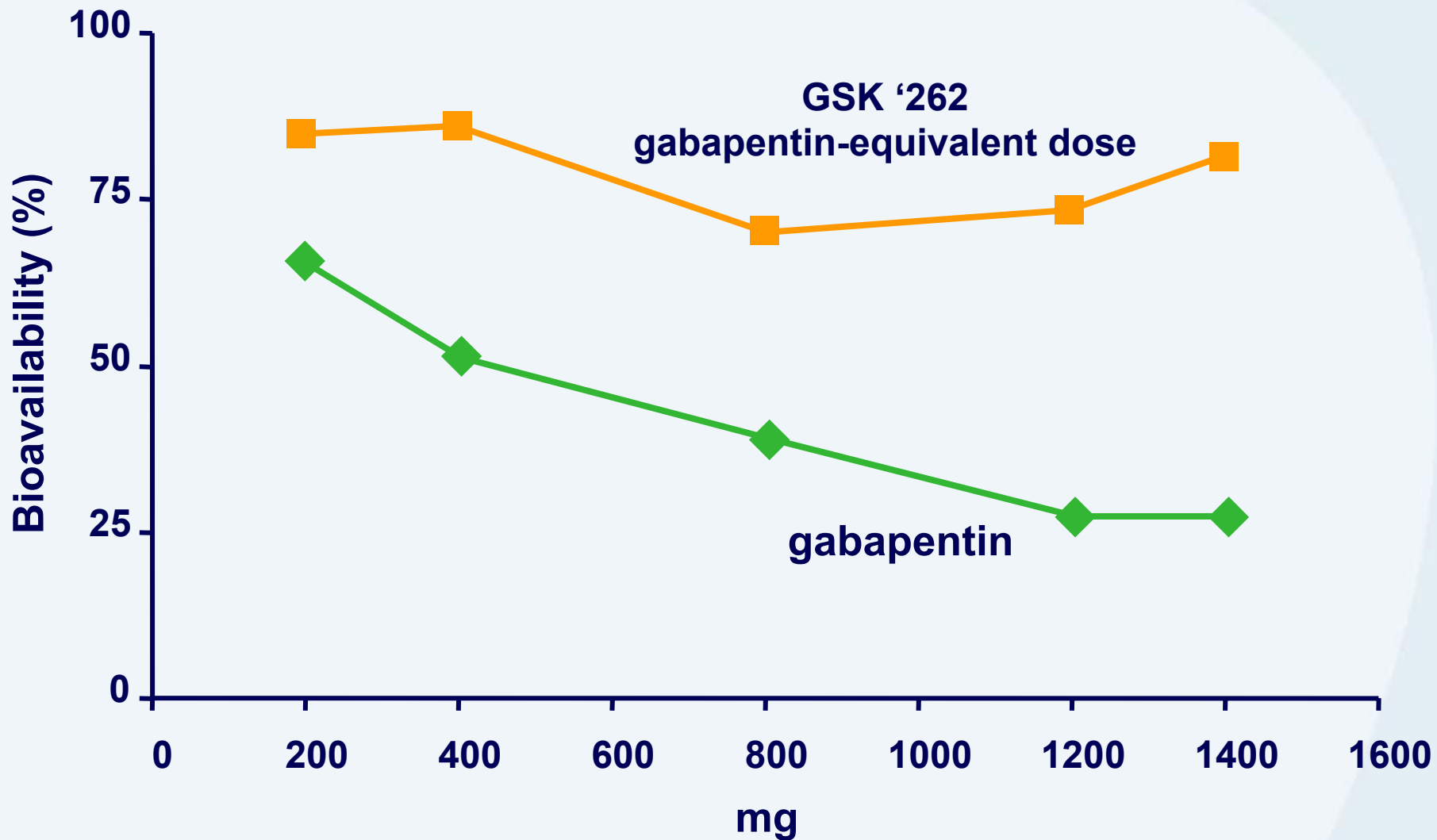
gabapentin



GSK '262

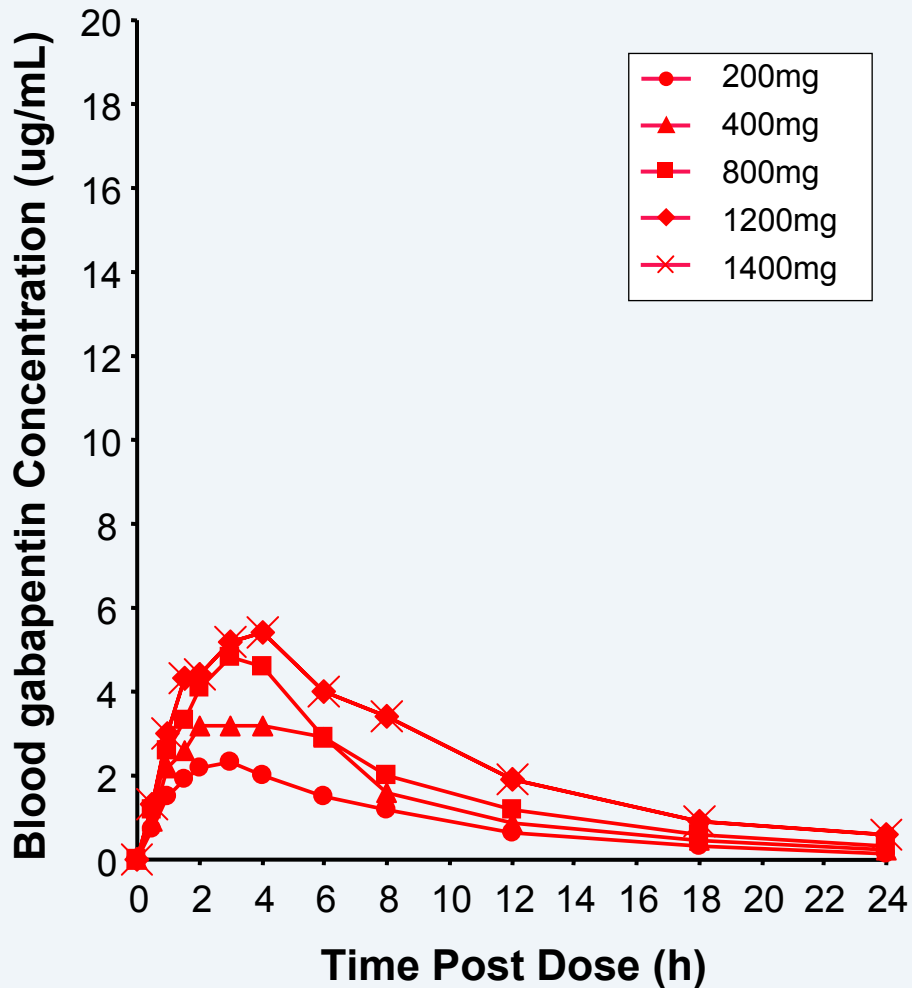
- Actively transported by monocarboxylate transporters (MCT) and Na-dependent multi-vitamin transporters (SMVT)
- Well-absorbed throughout intestinal tract
- Rapidly converted to gabapentin and safe metabolites

GSK '262 improves gabapentin bioavailability



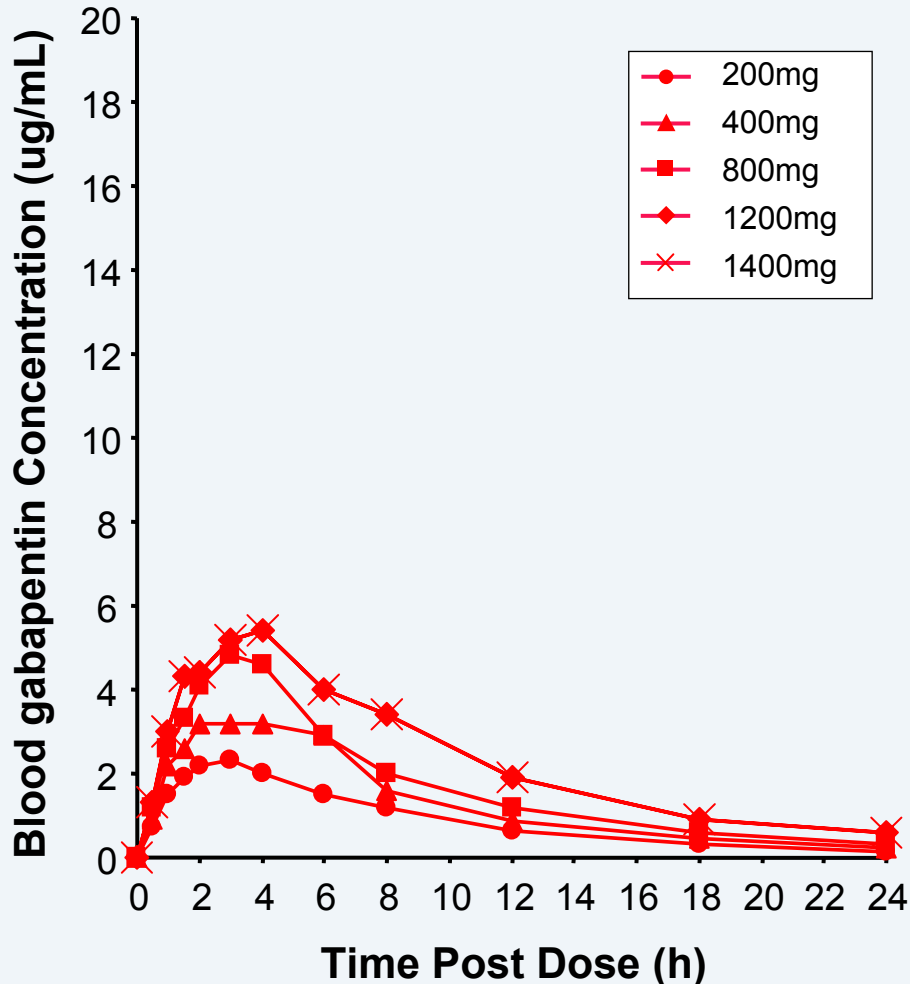
Gabapentin exposure is non-dose proportional

gabapentin

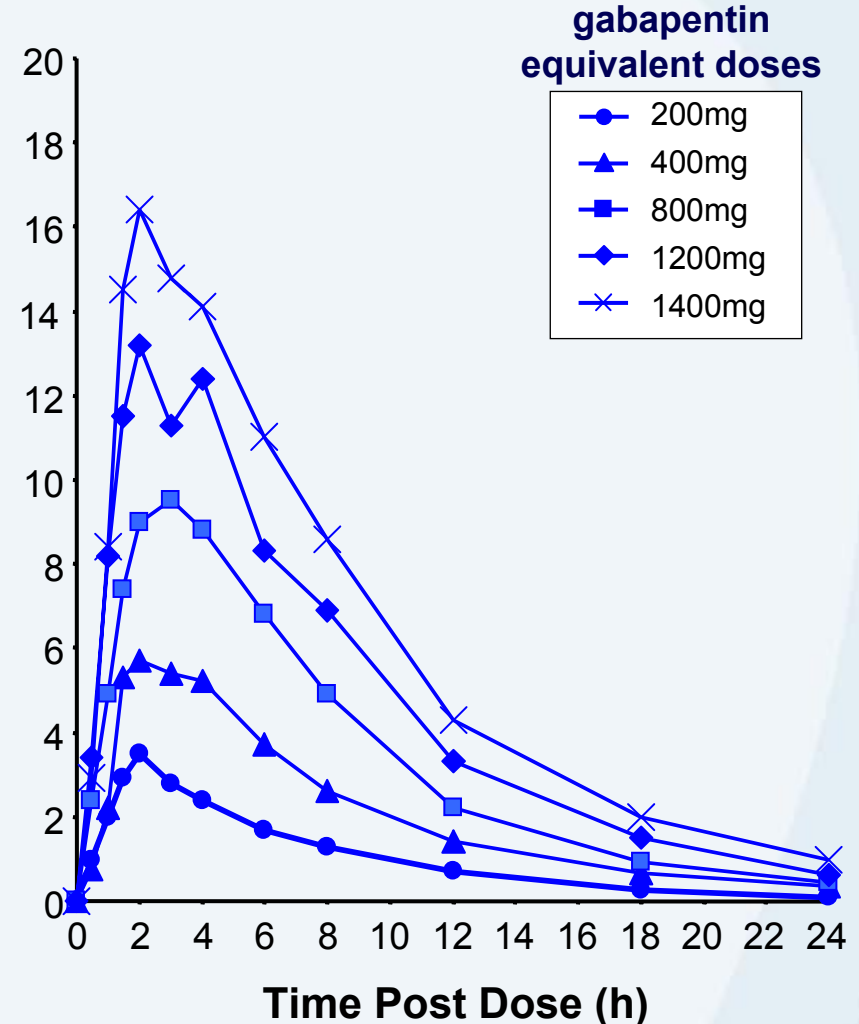


GSK '262 achieves dose-proportional exposure

gabapentin



GSK '262



GSK '262 is a major advance over gabapentin

- More reliable absorption
- Dose-proportional plasma drug exposure
- Longer duration of plasma drug exposure

=

Opportunity for greater efficacy

GSK '262

```
graph TD; GSK["GSK '262"] --- RLS["Restless Legs Syndrome (RLS)"]; GSK --- MP["Migraine Prophylaxis"]; GSK --- NP["Neuropathic Pain"]; GSK --- MD["Mechanism for Differentiation"];
```

**Restless Legs Syndrome
(RLS)**

Migraine Prophylaxis

Neuropathic Pain

**Mechanism for
Differentiation**

Pain has multiple aetiologies

Inflammation/Trauma

Lower Back Pain

Rheumatoid Arthritis

Osteoarthritis

Migraine

Dental

Neuropathic

Diabetic Neuropathy

Post-herpetic Neuralgia

Nerve Injury

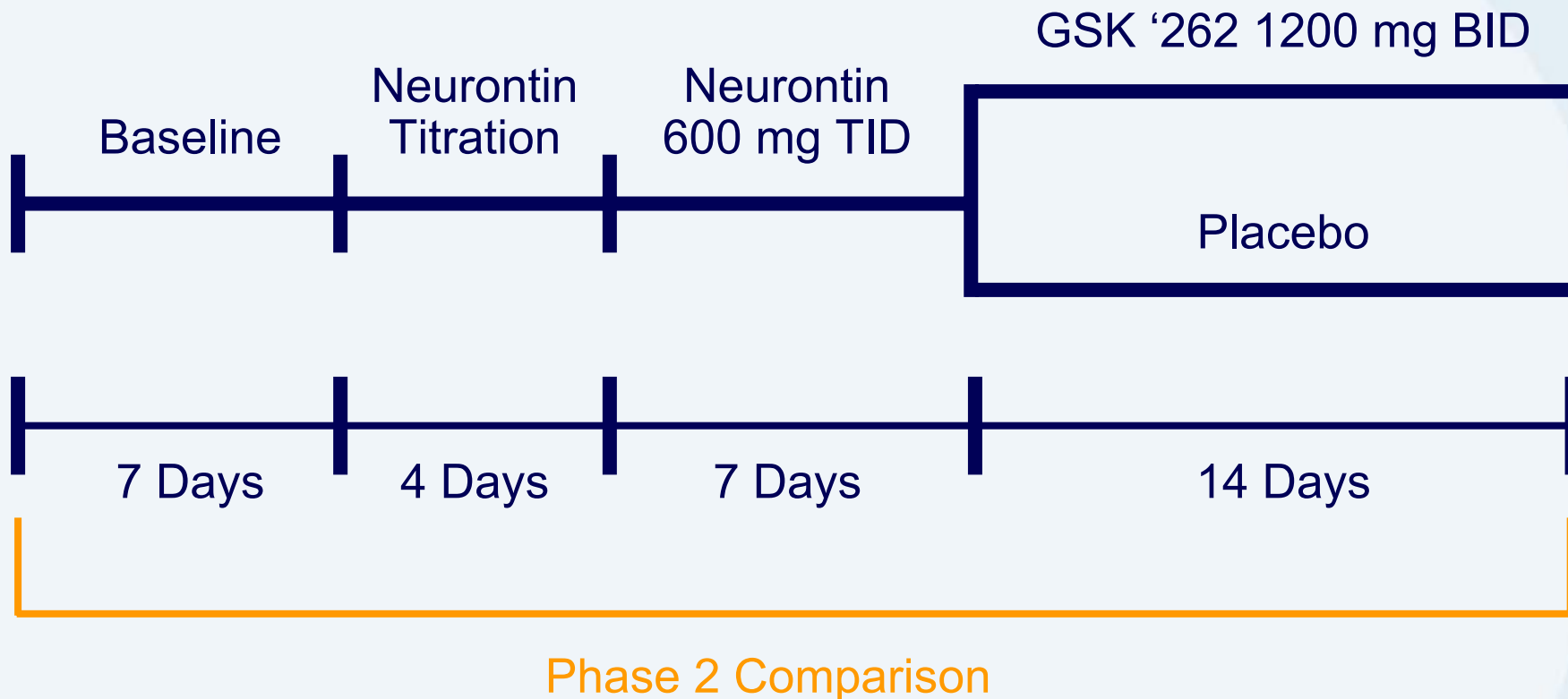
Neuropathic pain – current treatment options

- Antiepileptics
 - gabapentin
 - pregabalin (Lyrica)
- Local anesthetics
 - topical lidocaine
- Antidepressants
 - amitriptyline
 - venlafaxine (Effexor)
 - duloxetine (Cymbalta)

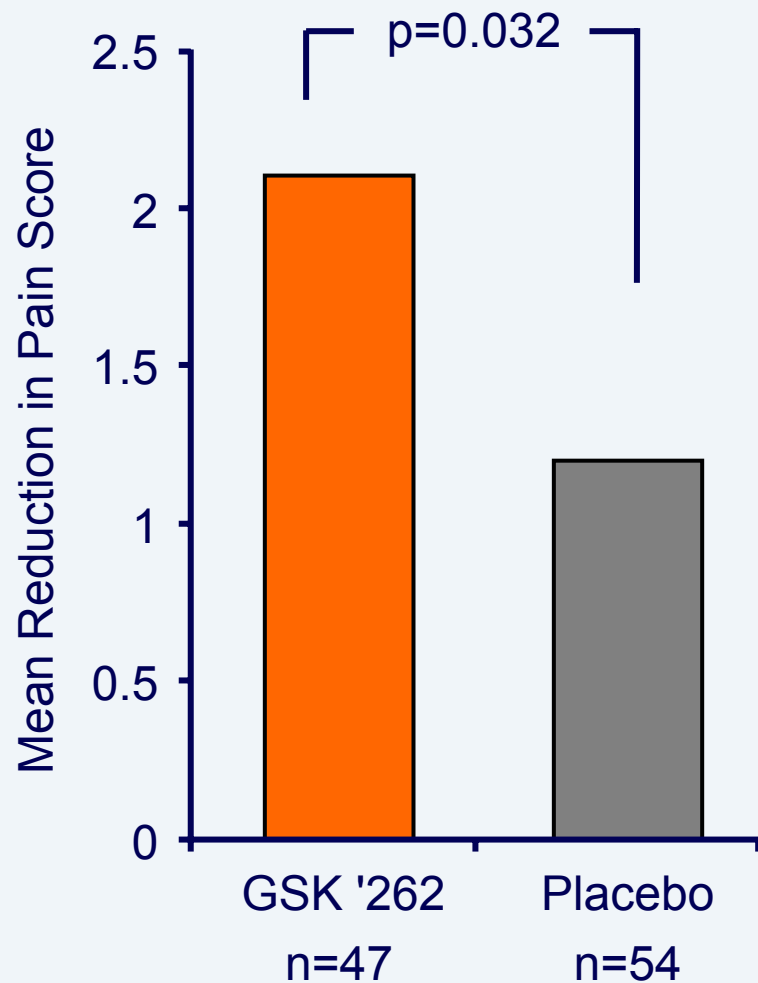
Considered
Gold Standard

<u>FDA Approved</u>		<u>Not Approved</u>
<u>PHN</u>	<u>PDN</u>	
✓		
✓	✓	
✓		
		✓
	✓	✓

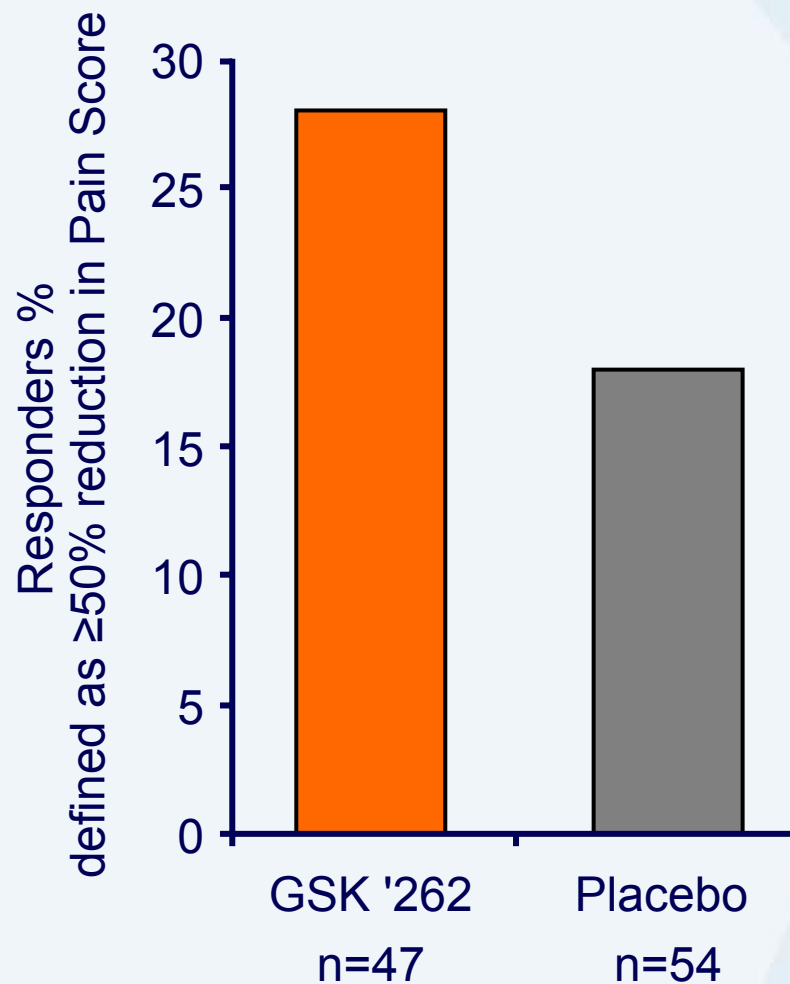
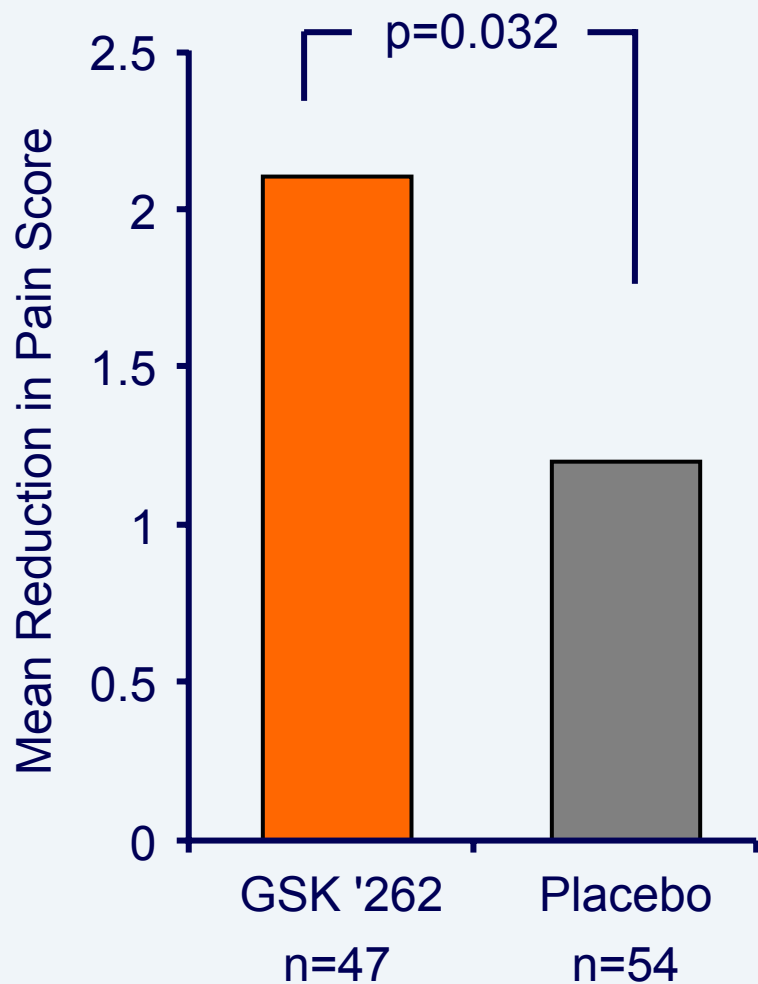
GSK '262 – Phase II POC study in PHN



GSK '262 – Phase II in PHN results



GSK '262 – Phase II in PHN results



Next steps – Neuropathic pain

Start next studies Q1 2008; read out 2009 to inform Phase III design

Next steps – Neuropathic pain

Start next studies Q1 2008; read out 2009 to inform Phase III design

- Dose-range finding studies
 - PHN
 - 14 week study; n=380; 1200, 2400 or 3600mg/day GSK '262 vs placebo
 - PDN
 - 12 week study; n=392; 1200, 2400 or 3600mg/day GSK '262 vs placebo and pregabalin (+ve control)

Next steps – Neuropathic pain

Start next studies Q1 2008; read out 2009 to inform Phase III design

- Dose-range finding studies

- PHN

- 14 week study; n=380; 1200, 2400 or 3600mg/day GSK '262 vs placebo

- PDN

- 12 week study; n=392; 1200, 2400 or 3600mg/day GSK '262 vs placebo and pregabalin (+ve control)

- Differentiation study in PHN patients who have not responded to treatment with gabapentin

- 2 period cross-over design (1200 or 3600mg/day GSK '262) in 164 PHN patients who have baseline pain intensity scores >4 after 6 weeks of gabapentin 1800mg/day

GSK '262

```
graph LR; GSK["GSK '262"] --- RLS["Restless Legs Syndrome (RLS)"]; GSK --- MP["Migraine Prophylaxis"]; GSK --- NP["Neuropathic Pain"]; GSK --- MD["Mechanism for Differentiation"];
```

**Restless Legs Syndrome
(RLS)**

Migraine Prophylaxis

Neuropathic Pain

**Mechanism for
Differentiation**

Migraine prophylaxis



- 30m migraine patients in the US
- Fewer than 20% of patients who experience two or more migraines a month are on a prophylaxis regimen
 - Cited reasons:
 - **Lack of efficacy** in reducing frequency or severity of attacks
 - **Side effects** (cognitive impairment, dizziness and paresthesias, etc.)

Gabapentin has shown efficacy in migraine prophylaxis*

- Efficacy in reducing the frequency of migraine attacks
 - Di Trapani et al. Clin Ther 2000;151:145-8.
 - Mathew et al. Headache 2001;41:119-128.
- Efficacy in reducing chronic daily headaches – a severe form of headache
 - Spira and Beran. Neurology 2003;61:1753-1759.

Next steps – migraine prophylaxis

- Expect to initiate pivotal Phase III dose ranging efficacy and open long term studies in 2H 2008
 - Following agreement with FDA
- Pivotal Phase III dose-range efficacy and safety studies
 - 2 x 12 week placebo controlled dose-ranging studies
- Long-term safety study
 - De novo and roll-over patients from pivotal DR studies

GSK '262

```
graph LR; GSK('GSK '262') --- RLS('Restless Legs Syndrome (RLS)'); GSK --- MP('Migraine Prophylaxis'); GSK --- NP('Neuropathic Pain'); GSK --- MD('Mechanism for Differentiation');
```

**Restless Legs Syndrome
(RLS)**

Migraine Prophylaxis

Neuropathic Pain

**Mechanism for
Differentiation**

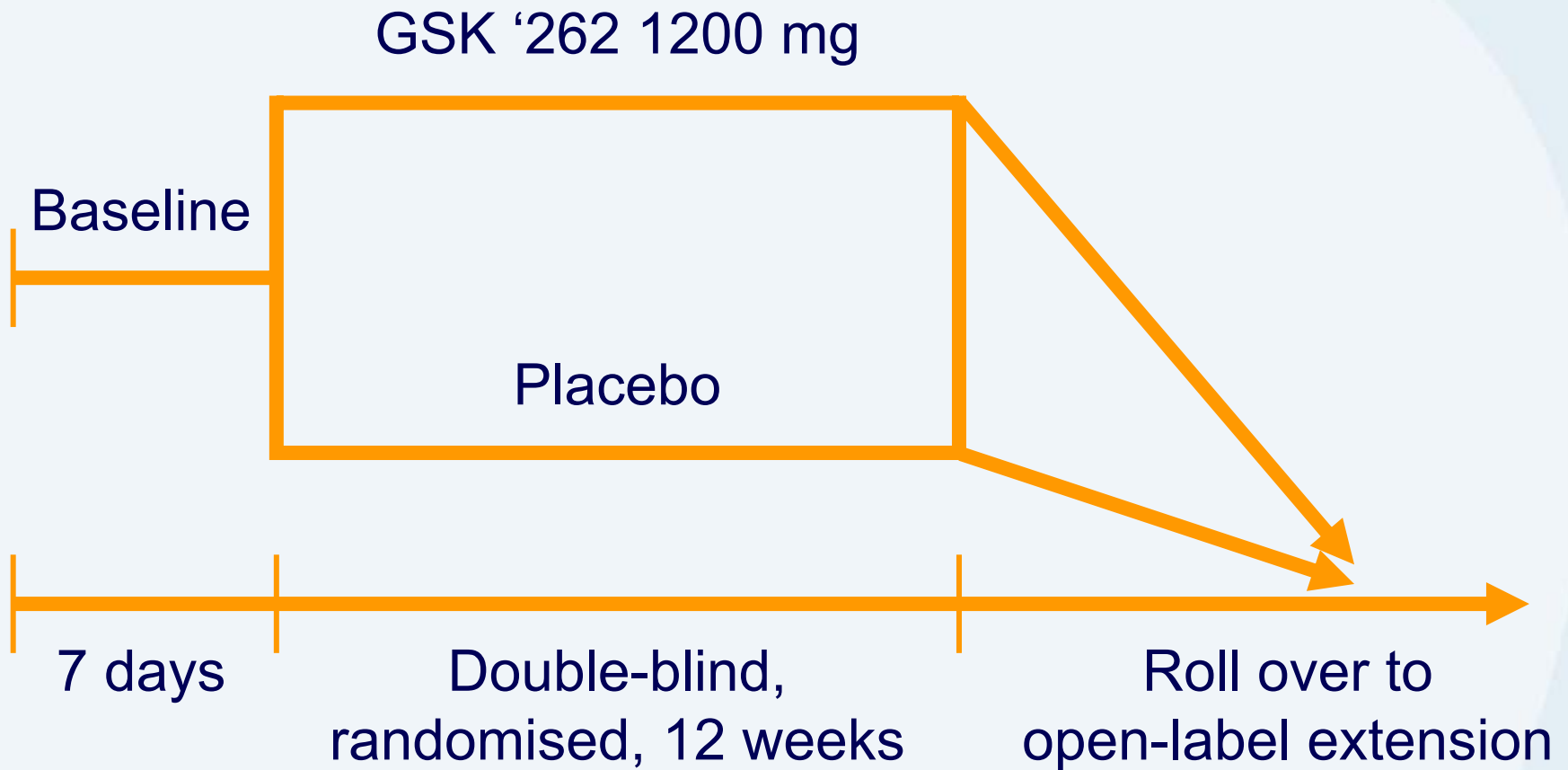
RLS – significant market opportunity

- Awareness of RLS has increased dramatically
 - 2-3% of the general population have symptoms that impair QoL
- Dopamine agonists now the accepted treatment
 - There is room for improvements on tolerability and side effects

GSK '262 – RLS phase III development plan

- Confirmation of efficacy
 - XP052 (1200mg vs PI) n=222, study complete
 - XP053 (600,1200mg vs PI), data Q1 08
 - XP060 (maintenance of effect), data Q1 08
- Long-term safety
 - XP055 (Open Label Rollover), study on-going
- Other required studies to meet regulatory requirements
 - QTc, PK/PD and Driving Study
- US NDA filing expected: 3Q2008

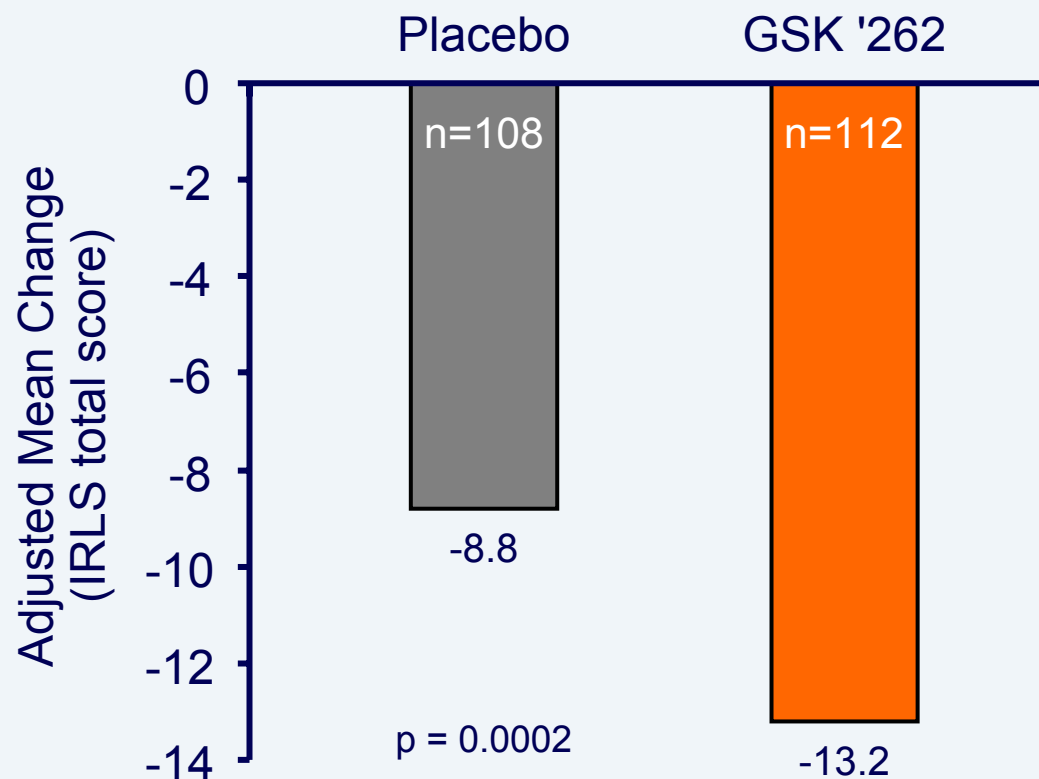
GSK '262 – phase III study in RLS



GSK '262 – phase III

Strong efficacy in RLS

Change from Baseline IRLS Rating Scale Total Score at Week 12 LOCF



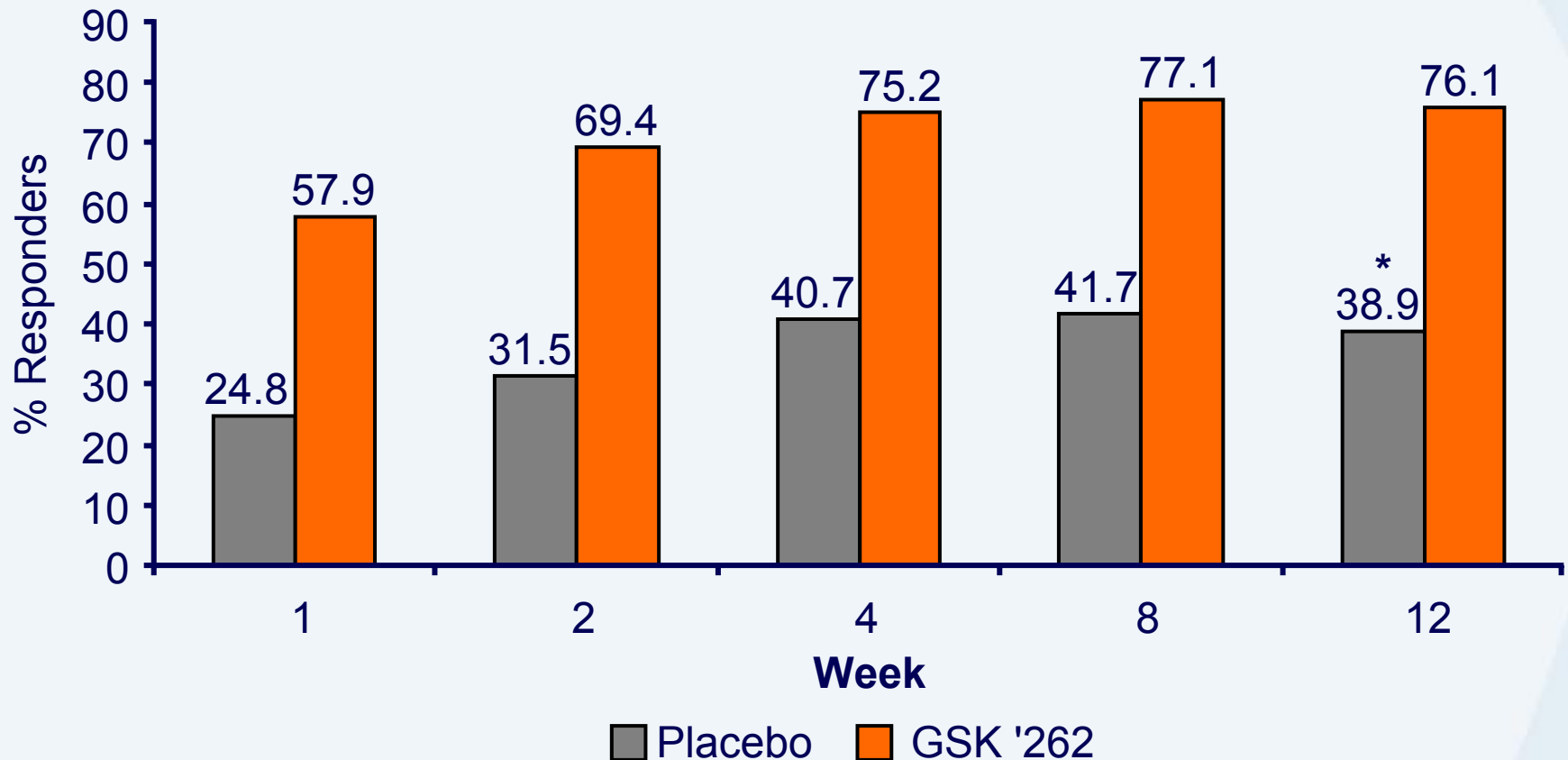
International RLS Rating Scale (IRLS) = 10 questions rated 0-4 by the clinician

GSK '262 – phase III in RLS

High rate of responders with sustained improvement

CGI-I Responder Analysis

Response = “Much Improved” and “Very Much Improved”



*Odds ratio = 5 (95% C.I. 2.8, 9.2, $p < 0.0001$).
Business Alliance with Xenoport, Inc.

GSK '262 – phase III in RLS tolerability profile

- GSK '262 was well tolerated with a side effect profile similar to gabapentin
- 8% of GSK '262 treated patients withdrew from study due to AEs vs. 3% for placebo treated patients
- As expected, somnolence (26.5%) and dizziness (19.5%) were the most frequently reported AEs. AEs were generally mild or moderate in severity
 - No evidence of drug-related compulsive behaviors, sudden sleep attacks or augmentation
- There were no SAEs in GSK '262 treated patients

Next steps – RLS

- Complete Phase III development plan
 - Expect filing 3Q2008

Next steps – RLS

- Complete Phase III development plan
 - Expect filing 3Q2008
- Areas for further differentiation with additional studies
 - Benefits in sleep
 - 2 polysomnography studies starting 2H08
 - Painful symptoms of RLS
 - Improved tolerability vs. dopamine agonists
 - Efficacy in co-morbid/secondary RLS (e.g. diabetes)

Late-stage pipeline

- *Trexima*
- *Requip XL* for Parkinson's
- *Lunivia* in Europe – filed in July
- *Lamictal XR* for epilepsy: “approvable” Sept. '07
- rosiglitazone XR in Alzheimer's disease
- GSK '262
 - Neuropathic pain (Phase II)
 - Migraine prophylaxis (Phase III)
 - RLS expected filing in 2008



GlaxoSmithKline