

Phase III Sativex[®] MS Spasticity Trial



Study GWSP0604
Preliminary Results

11 March 2009



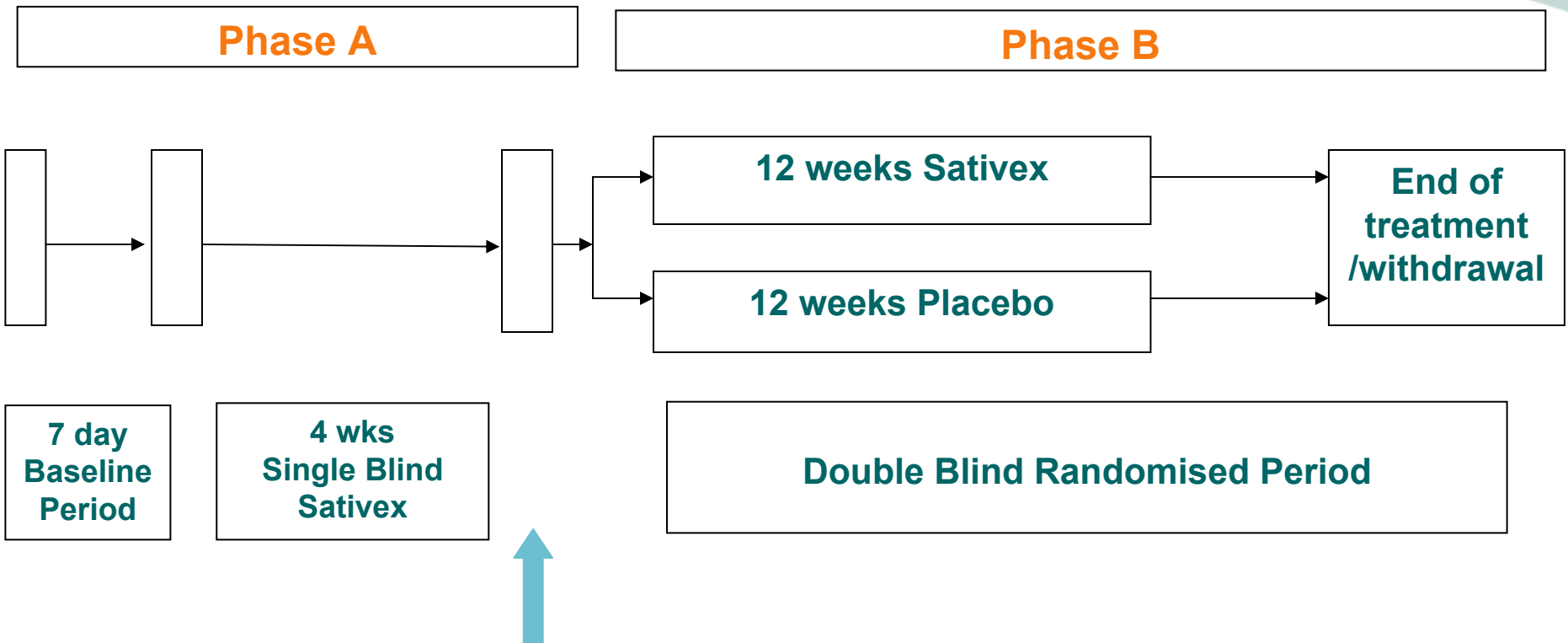
Study Rationale: Route to Regulatory Approval

- In previous regulatory application, quality and safety data were sufficient to support approval
- Regulators identified a key outstanding efficacy issue
 - Target MS patients have advanced disease and are treatment-resistant
 - Hence, not all patients have capacity to respond
 - Benefit seen in “responders” is masked by mean data across all patients
 - Regulators wish to be able to identify Sativex responders in the first 4 weeks of treatment and to confirm that improvements gained by such responders over a further 12 week period is significantly greater than placebo
 - “Post hoc” analyses of responders data in previous submission showed strong results ($p=0.015$)
 - Regulators asked GW to re-confirm this in a prospectively planned study
- The regulators gave GW clear guidance on the design of the required study
 - “Enriched design”
 - First identify responders over a 4 week period, and then analyse the effect of Sativex vs placebo on those responders over a further period of 12 weeks

Study Design

General:	Placebo-controlled, randomised, parallel group study
Patients:	People with Multiple Sclerosis and spasticity who have failed to gain adequate relief from existing anti-spasticity medication and who demonstrate a capacity to respond to treatment
Duration:	4 weeks single blind Sativex followed by 12 weeks double blind randomised period
Primary Endpoint:	Mean change in spasticity measured on the 0-10 Numeric Rating Scale
Secondary Endpoints:	Responder Analysis, Spasm, Sleep, Patient & Physician Global Impression of Change, etc

GWSP0604 Study Design



Notes: Patients must achieve >20% improvement to be randomised
The dose taken remains stable from Phase A to Phase B

GWSP0604: Demographics

Age (yrs)	48.5 years
Gender – Male	40%
Female	60%
Type of MS	
➤ Primary Progressive	16%
➤ Secondary Progressive	50%
➤ Relmitting/Relapsing	32%
➤ Progressive Relapsing	2%
Duration of MS	12.14 years
Duration of Spasticity	7.17 years
Mean Baseline Spasticity (0-10 NRS)	7.04
Baseline EDSS	6

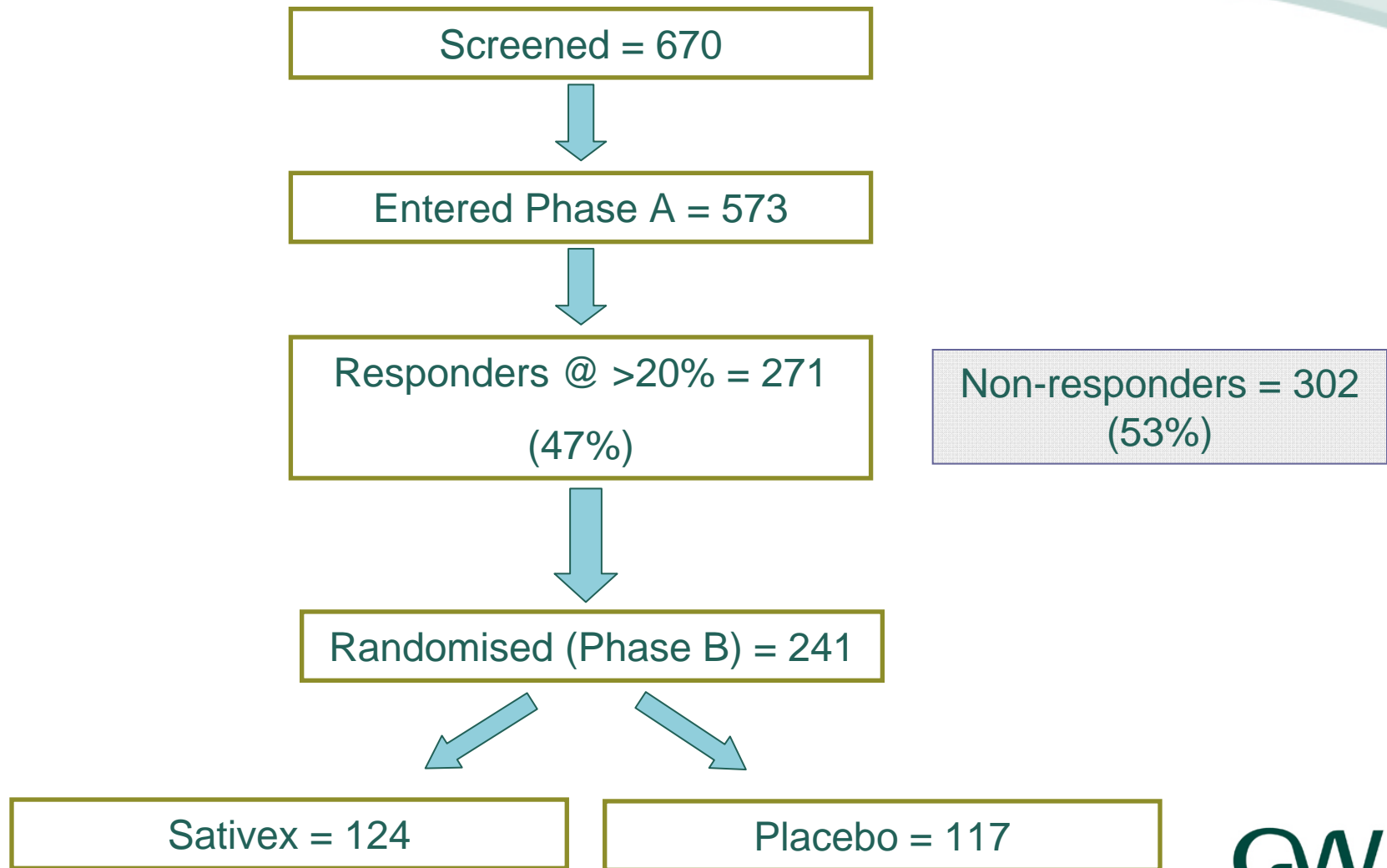
Treatment-resistant MS patients with significant disability and unmet medical need

GWSP0604: Background Medication

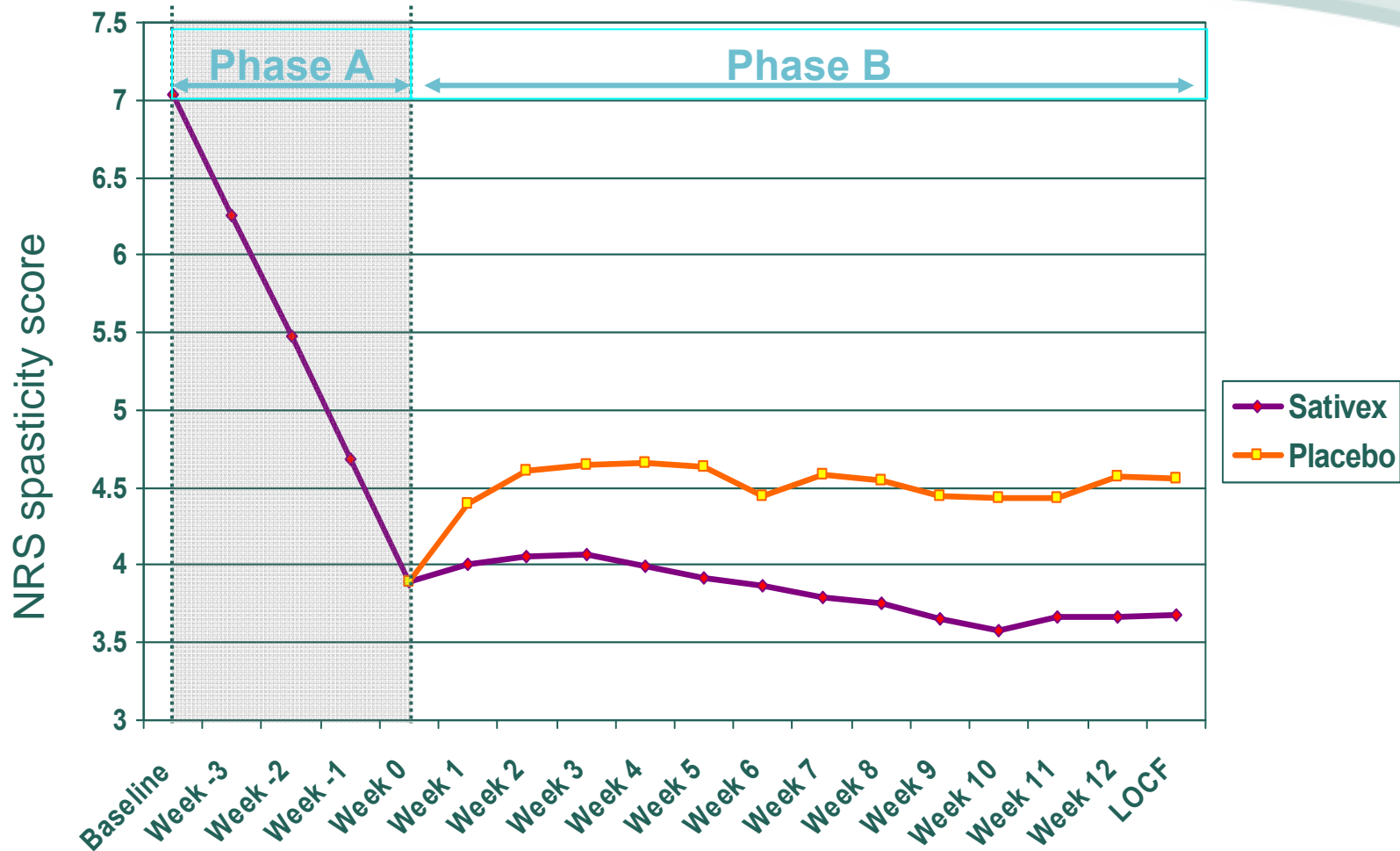
Medication	%
Baclofen	57%
Tizanidine	19%
Benzodiazepines	17%
Others (gabapentin, dantrolene, botulinum toxin)	12%
Disease modifiers	53%

All patients have previously failed to respond to anti-spasticity therapy and continue to take their pre-existing background medication throughout the study

GWSP0604: Responders in Single-Blind Period (Phase A)



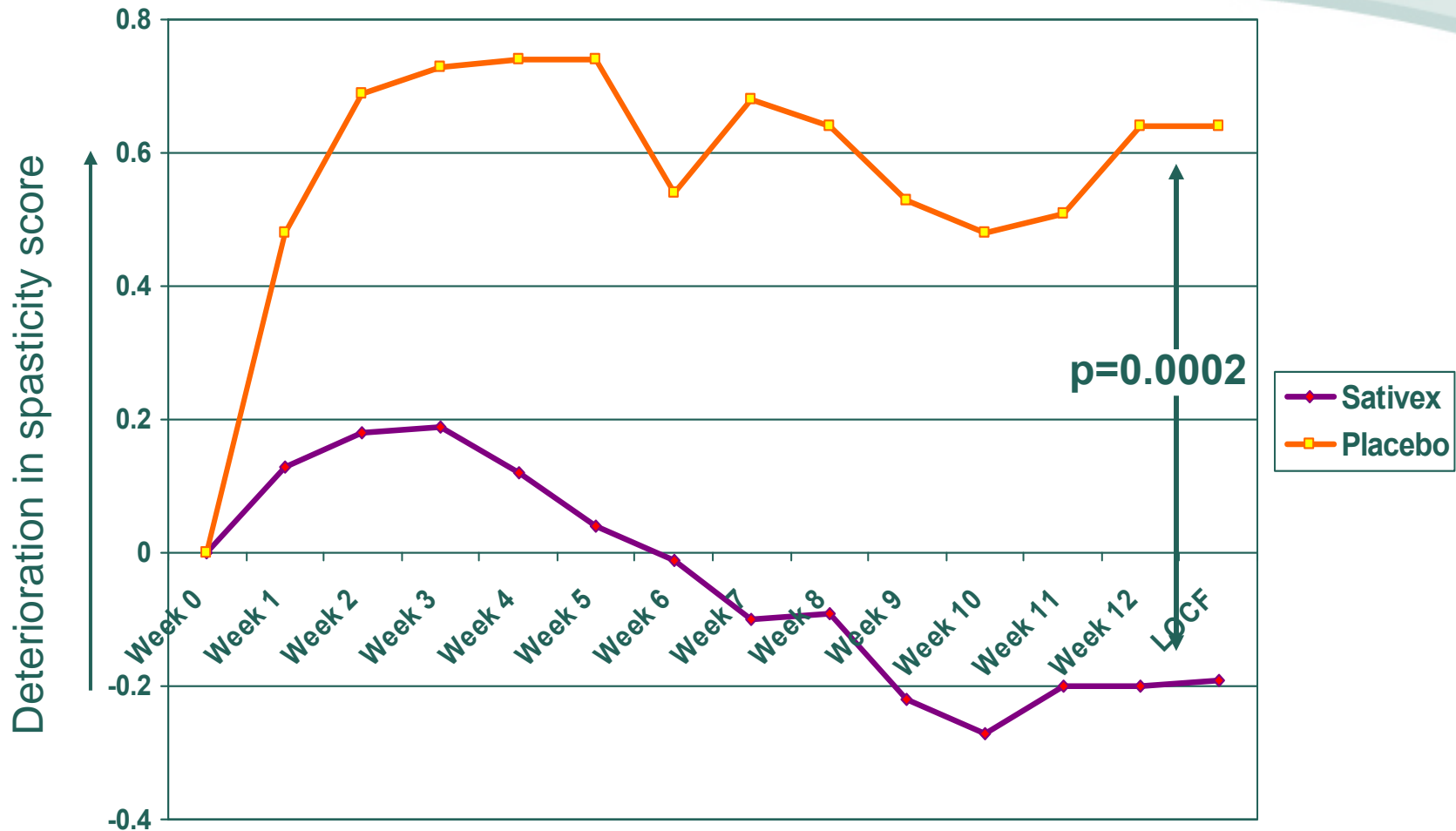
GWSP0604: NRS Spasticity scores over time



Mean 48% improvement in spasticity on Sativex over 16 weeks

GWSP0604: Primary Endpoint

Phase B Change in Spasticity scores

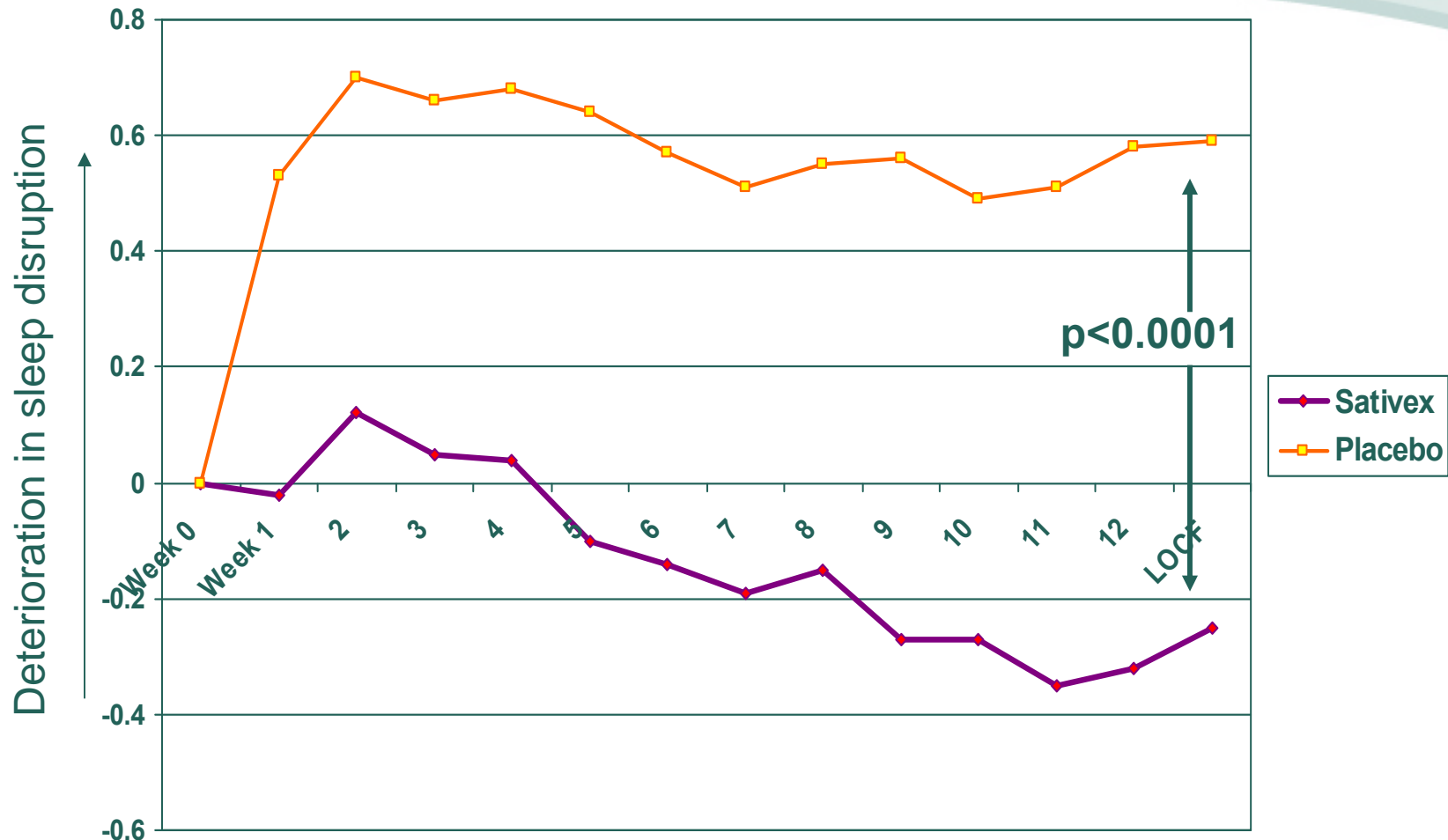


Baseline scores

Sativex: 3.87

Placebo: 3.92

GWSP0604: Secondary Endpoint: Change in Sleep Disturbance scores



Baseline scores: Sativex: 1.96
Placebo: 2.07

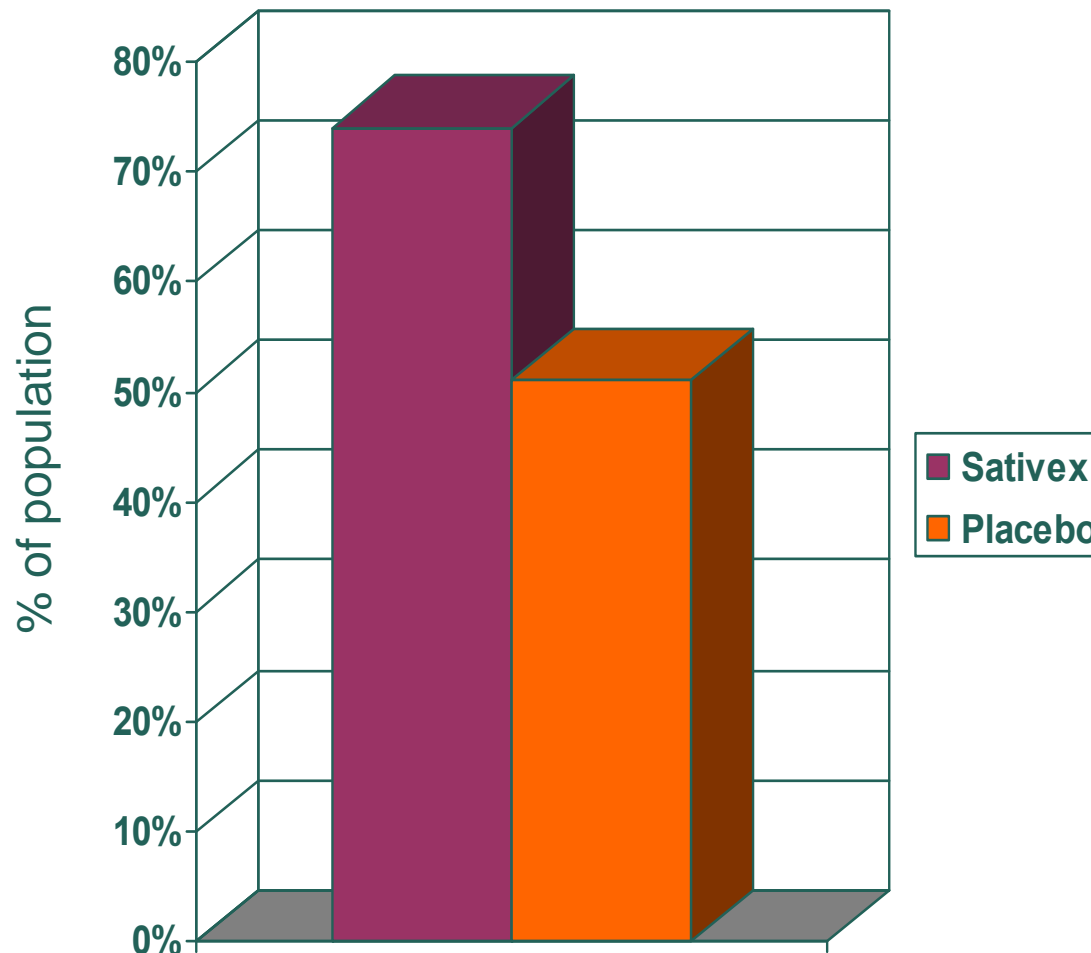
GWSP0604: Secondary Endpoint Change in Spasm Frequency scores



Baseline scores: Sativex: 5.61
Placebo: 5.29

GWSP0604: Secondary Endpoint Responder Analysis: $\geq 30\%$ Response

$p=0.0003$



- A responder is defined as the change from the original study baseline
- All patients had been refractory to other anti-spasticity treatments
- 92/124 Sativex patients showed a response of at least 30% following this treatment regimen

GWSP0604: Other Positive Secondary Endpoints

- Patient global impression of change in spasticity (p=0.023)
- Physician global impression of change in spasticity (p=0.005)
 - Provides useful objective verification of response

Excellent Safety Profile: Adverse Events at > 3%

Adverse Event	Phase A period of Study SP0604 (n=573)		Guidance from previous MS studies (n=663)
Dizziness	13%		32%
Fatigue	6%		12%
Somnolence	5%		8%
Nausea	4%		12%
Dry Mouth	4%		8%
Urinary Infection	3%		9%
Vertigo	3%		4%

Improved safety profile resulted from modified dose titration regimen employed in the study

Randomised Withdrawal Study of Sativex[®] in MS Spasticity



Study GWSP0702
Preliminary Results

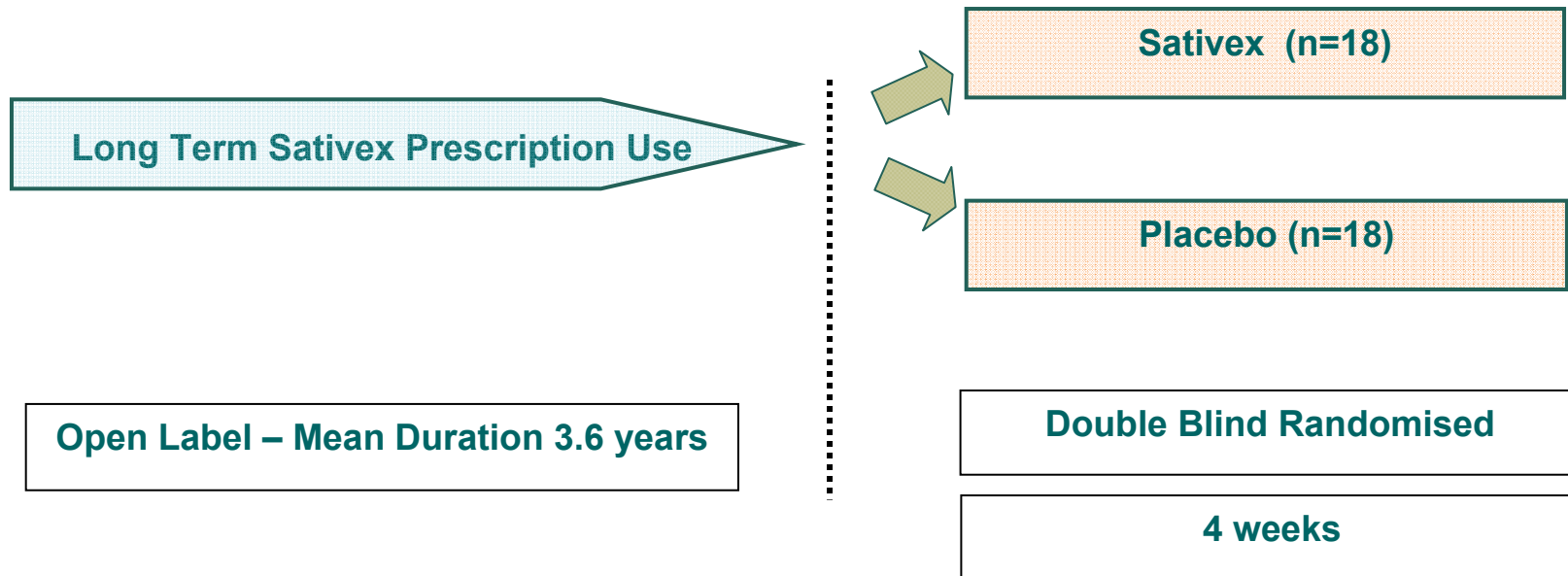
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Study Rationale: The Regulatory Perspective

- In previous application, GW presented substantial long term open label data in 444 patients exposed to Sativex for a mean of 455 days
 - Represents 554 patient-years of exposure
- Long term open label data showed evidence of maintenance of efficacy and no new safety signals
- Long-term open-label studies are not regarded by EU regulatory agencies as providing robust evidence of the maintenance of efficacy in the long term
- UK MHRA: “A randomised withdrawal trial following a period of open label treatment in patients considered to be responders would provide such information and would satisfy the need for controlled long term efficacy data”.

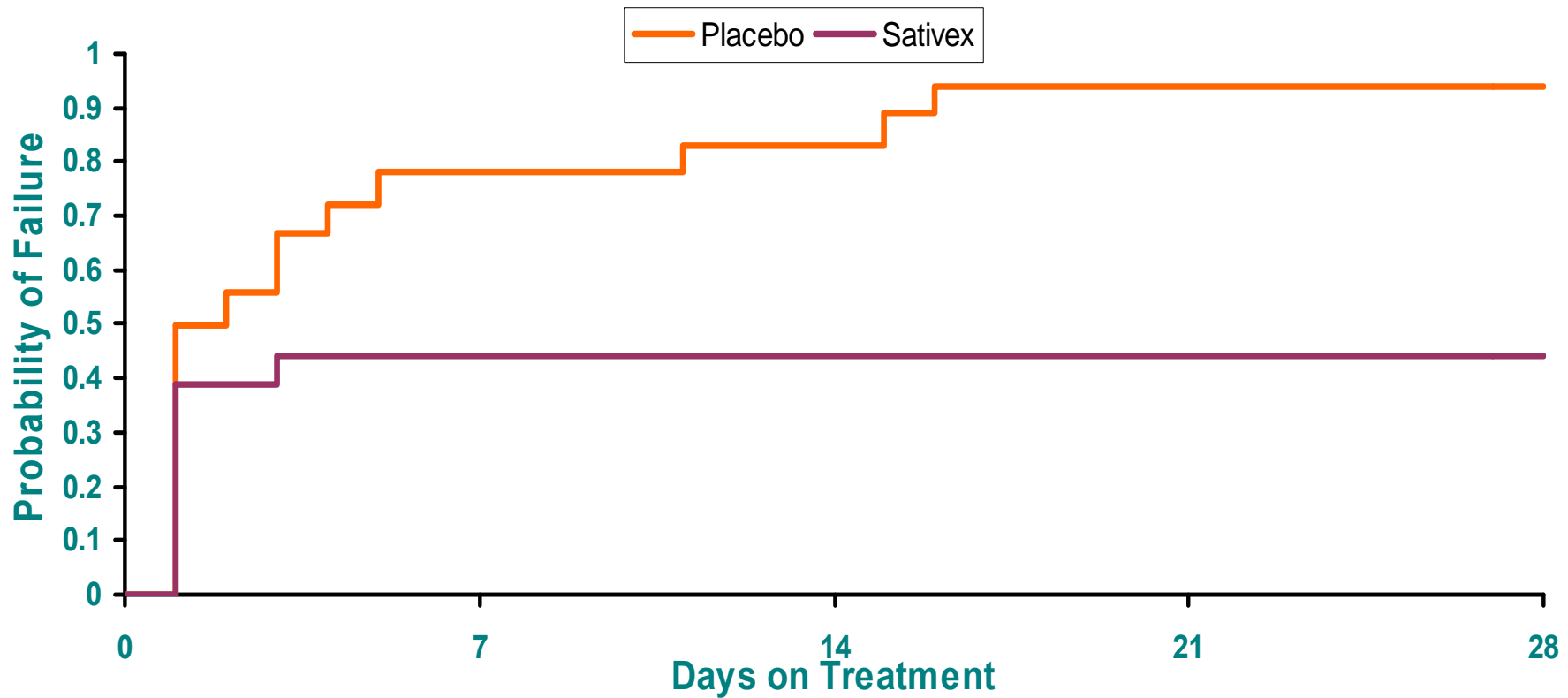
GWSP0702: Study Design



- All patients demonstrated clinically relevant response to Sativex whilst on long term prescription use
- Study dosing determined by dose level used in long term prescription use
- Recruitment for study was a challenge due to reluctance of patients to risk coming off Sativex for 4 weeks

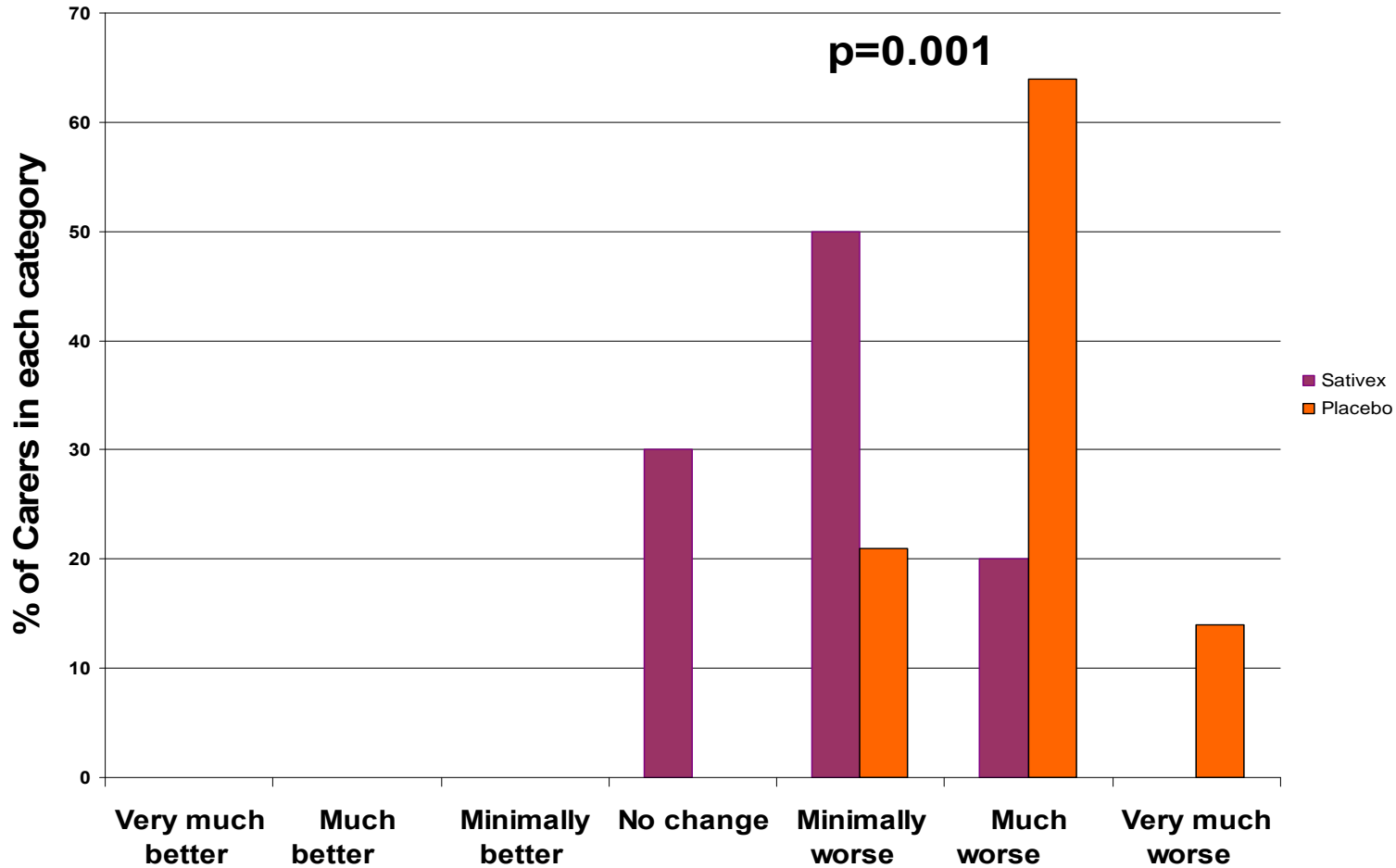
GWSP0702: Positive Primary Endpoint Time to Treatment Failure

Kaplan-Meier Plot: Time to Treatment Failure



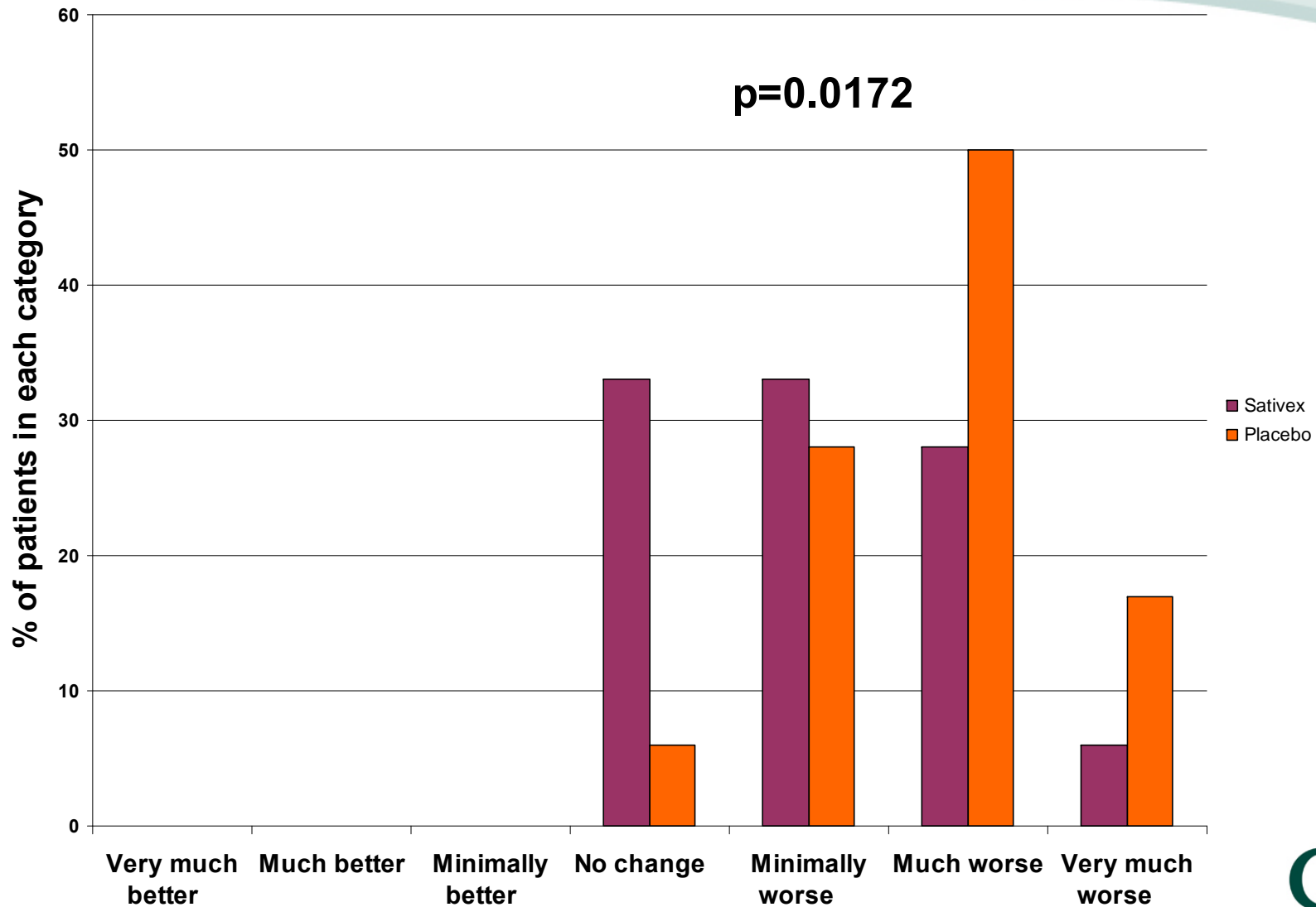
	Test	Chi-Square	p-value
Kaplan-Meier	Log-Rank	6.160	0.013

GWSP0702: Secondary Endpoint Carer Global Impression of Change - Functional Ability



Carers identify difference in functional ability

GWSP0702: Secondary Endpoint Patient Global Impression of Change



Summary

- Phase III study results provide robust evidence of efficacy of Sativex in MS Spasticity
- Phase III study expected to meet regulatory requirements for approval as stated in previous regulatory application
- Randomised withdrawal study provides significant evidence of long term efficacy in a study design recommended by regulators
- Sativex continues to show an excellent safety profile, which is further improved in this new data
 - Amended dose titration schedule reduces adverse event rate in early exposure
- In the last 6 months, GW has reported three positive Sativex studies incorporating a design modified from previous studies
 - New approach is producing consistent positive results
- Regulatory submission to be made Q2 09