Working hand in hand
with nature for a healthier world

Hyperimmune caprine sera -

A multi-platform therapeutic pipeline

by

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Scientific Background

- HICS is a product derived from a hyperimmune caprine source.
- HICS is composed of polyclonal antibodies (PAbs) and a range of smaller peptide components (Ps).
- PAbs are heterogeneous recognising multiple antigenic epitopes.
- HICS is able to modulate inflammatory responses - independently or synergistically with other components.
- HICS may have a greater therapeutic advantage over existing PAb strategies.
- HICS exhibits diverse molecular functioning and may explain its clinical efficacy.
- HICS has been shown to modulate the neuroendocrine system.

Manufacture of HICS

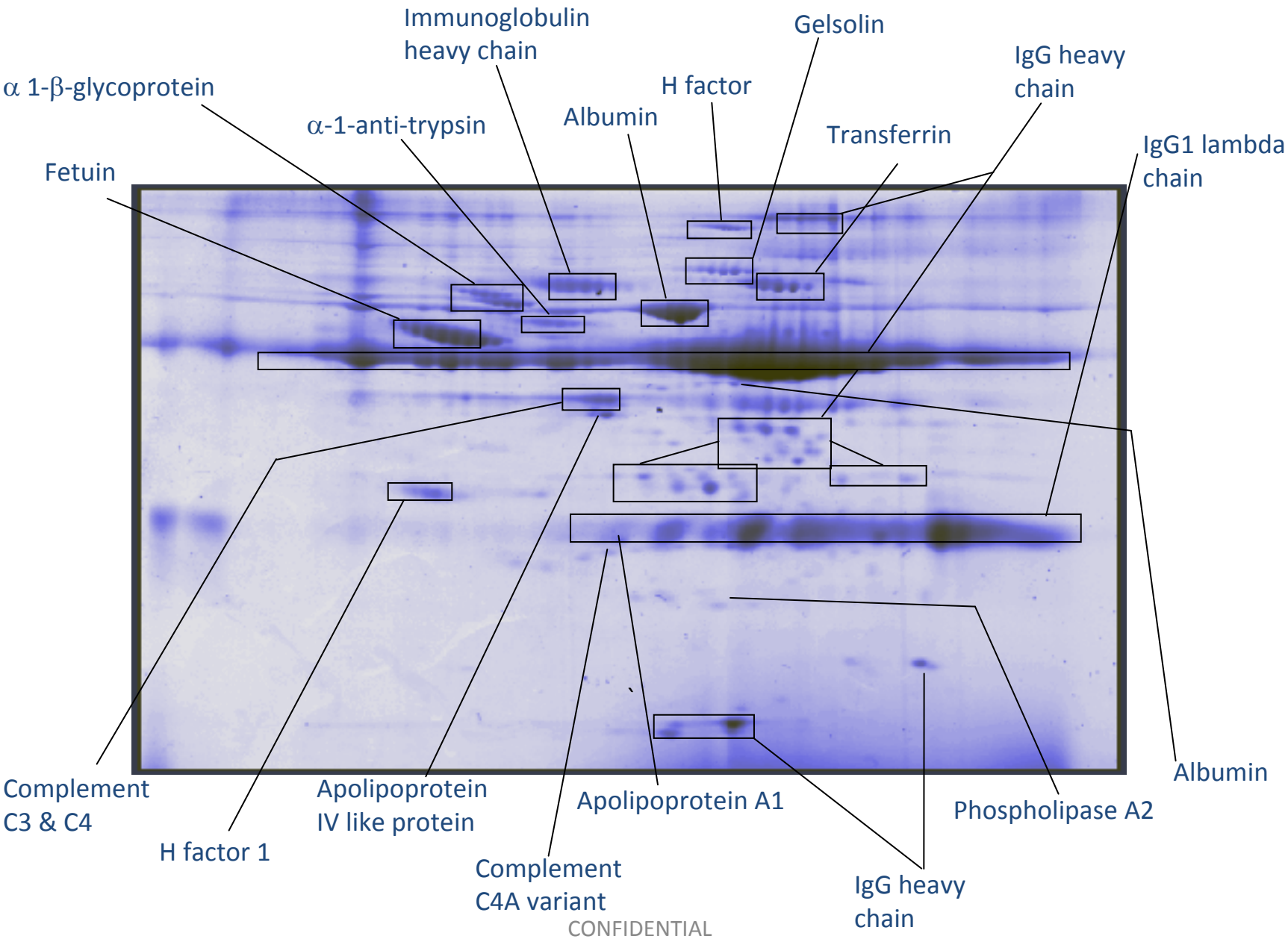
Inactivated HIV-1 IIIB
Lysate (NIH approved)

Inoculation
6 weeks

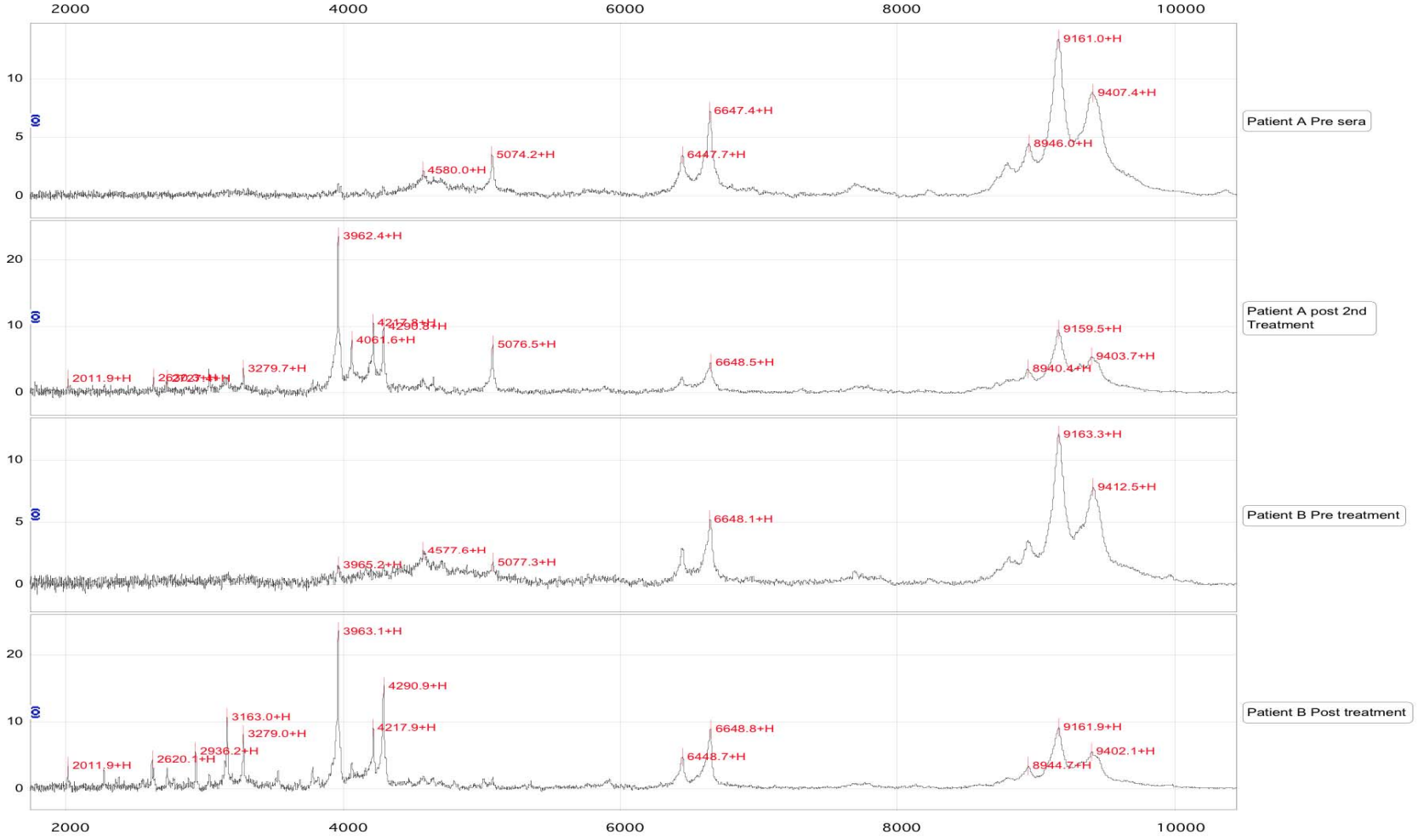
Category A - Prion Free

Bled
Every 4 weeks

Patented inactivation/extraction
MHRA regulated and approved
Nanofiltration
Serum extraction (4.5mg/ml)



Induction of protein expression in patients' sera following HICS treatment



Personal Experience

- Over 4-yrs of understanding of the use of HICS in a clinical setting.
- First patient - 28 yr old male with severe steroid resistant eczema, refractory to treatment for 18 yrs.
- Weekly treatment regimen followed by s.c. therapy every 2-3 weeks led to containment of the condition.
- No AE or SAE noted.
- Later expanded to treat a wide variety of patients with refractory diseases; **Alzheimer's Disease**, psoriatic arthropathy, psoriasis, RRMS, SPMS, rheumatiod arthritis, juvenile arthritis, **Motor Neuron Disease**, coeliac's disease, Crohn's disease, ulcerative colitis, metastatic adenocarcinoma of the colon, nodular sclerosis Hodgkin's lymphoma, prostate cancer, **sports injury**, CIDP, Hepatitis C, Dercum's disease, primary and secondary amyloidosis.

Safety History

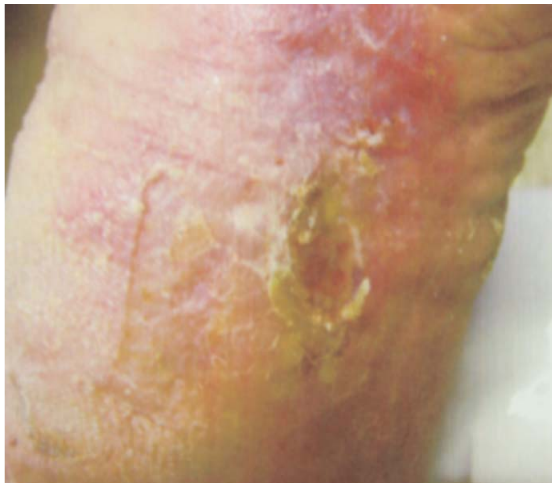
Over period of 12 years over 60,000 doses of HICS have been administered to in excess of 650 patients (including informed consent patients)

Minimal side effects have been recorded with only a transient red rash local to injection site in a proportion of cases (histamine response)

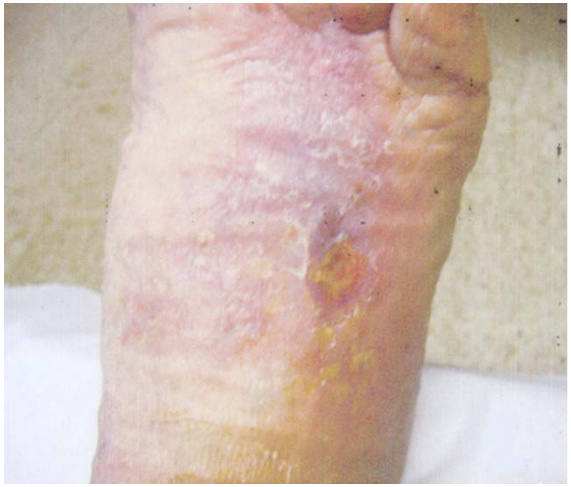
Where rashes occurred, these were treated by over-the-counter anti-histamine medication and were only present during the first few Injections and later resolved

Case Study (2003) - Hyperimmune Caprine Sera (HICS)

- Sex: F, Age 77yrs
- Dx HTN (2001), Type I DM
- Right foot ulcer - 20yrs
- No previous change 12 months
- Treatment - 1ml sc (4.5mg/ml HICS)/weekly for 3 weeks
- N=4



20/11/03



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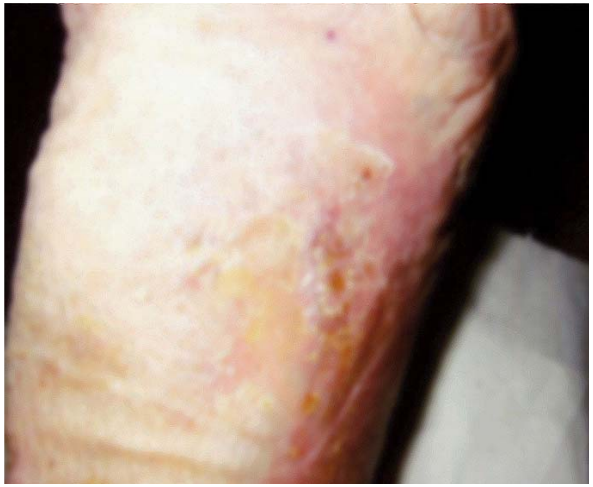


04/12/03

Update on Clinical Trial Status (I)

Established Late-Stage Diffuse Cutaneous Systemic Sclerosis (ELDSS)

Incidence 6,000 per yr and prevalence of 100,000 cases in the US, F>M

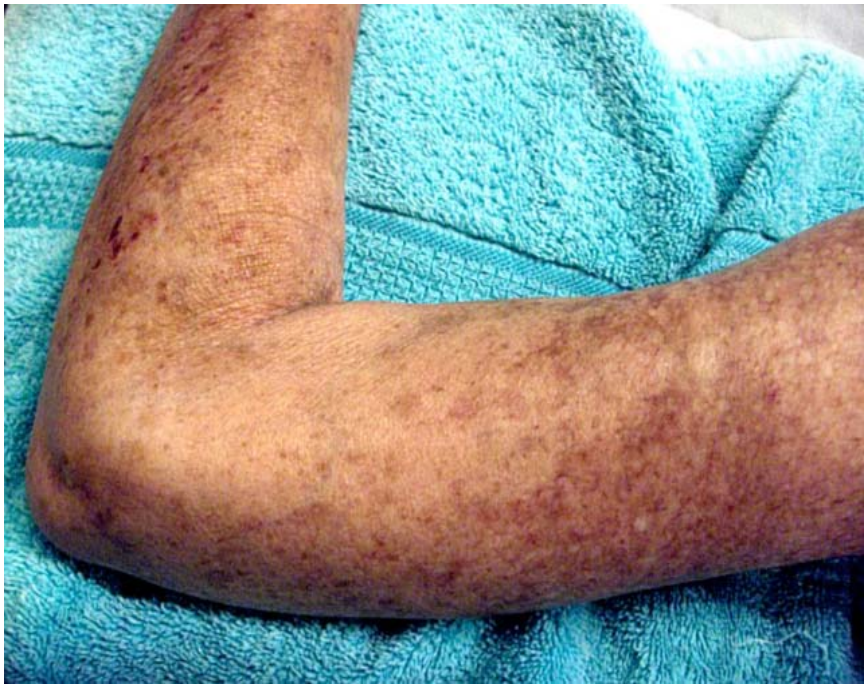
Multi-systemic disease characterised clinically by fibrosis of the skin, joints, muscles & internal organs.

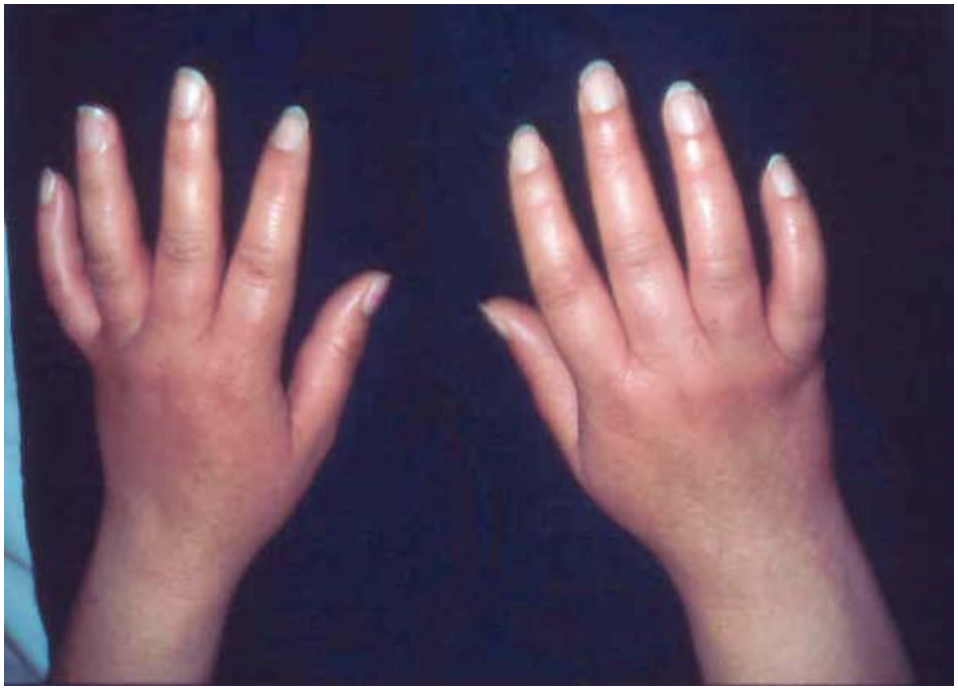
Pathogenesis

1. Inflammatory, vascular & fibroblast dysfunction
2. Sustained activation of a population of fibroblasts increased amounts of extracellular matrix in lesional tissues including the skin and internal organs
3. Impairment of the immune system
4. Cytokine and growth factor release (TGF-beta, CTGF, PDGF and MCP-1)

In 2005, patient with advanced systemic sclerosis treated with HICS on a compassionate basis. She experienced sustained improvement in mobility & there was a particular improvement in proximal muscle power & skin characteristics.

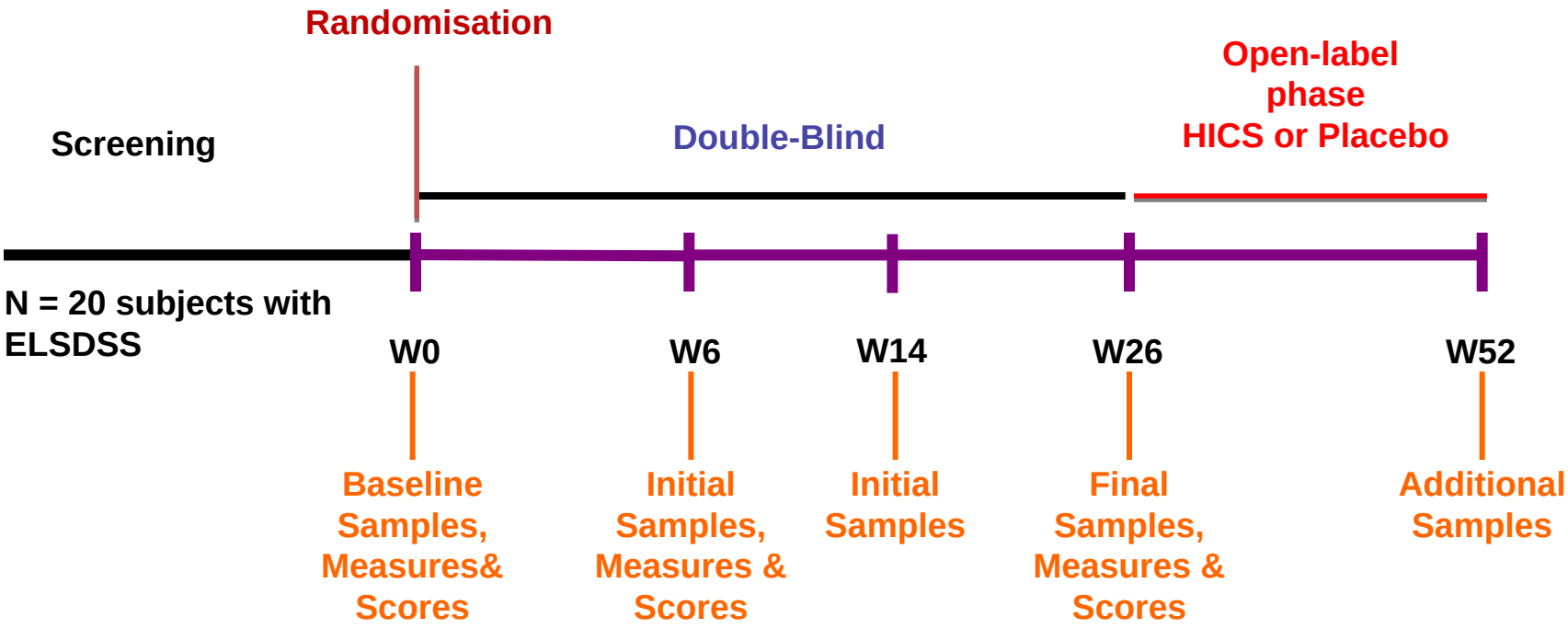
Diffuse Systemic Sclerosis





Scleroderma Trial Design & Treatment Schedule

Phase II Safety & Tolerability Study in **established late stage diffuse systemic sclerosis (ELSDSS)** assessing the effect of HICS



Groups

Group 1: Placebo

Group 2: 4.5mg/ml HICS 2 doses/ week

ELSDSS Trial Outcome Measures

Primary Endpoint Measures

- Safety and tolerability [Time Frame: Baseline, Week 6 & Week 26]
- Modified Rodnan Skin Score [Time Frame: Baseline, Week 6 & Week 26]

Secondary Endpoint Measures

- Scleroderma Health Assessment Questionnaire [Time Frame: Baseline, Week 6 & Week 26]
- Scleroderma UK Functional Score [Time Frame: Baseline, Week 6 and Week 26]
- Patient and Physician Global Assessment (VAS) [Time Frame: Baseline, Week 6 & Week 26]
- SF-36 (Short form 36) [Time Frame: Baseline, Week 6 & Week 26]
- MRC Sum Score [Time Frame: Week 0, Week 6 & Week 26]
- Biomarker measures

ELSDSS Trial Results - Primary Endpoints (I)

HICS was found to be a *safe and well-tolerated medication* when used in patients with ELSDSS at a dose of 4.5mg/ml given as a twice-weekly subcutaneous injection for 26 weeks.

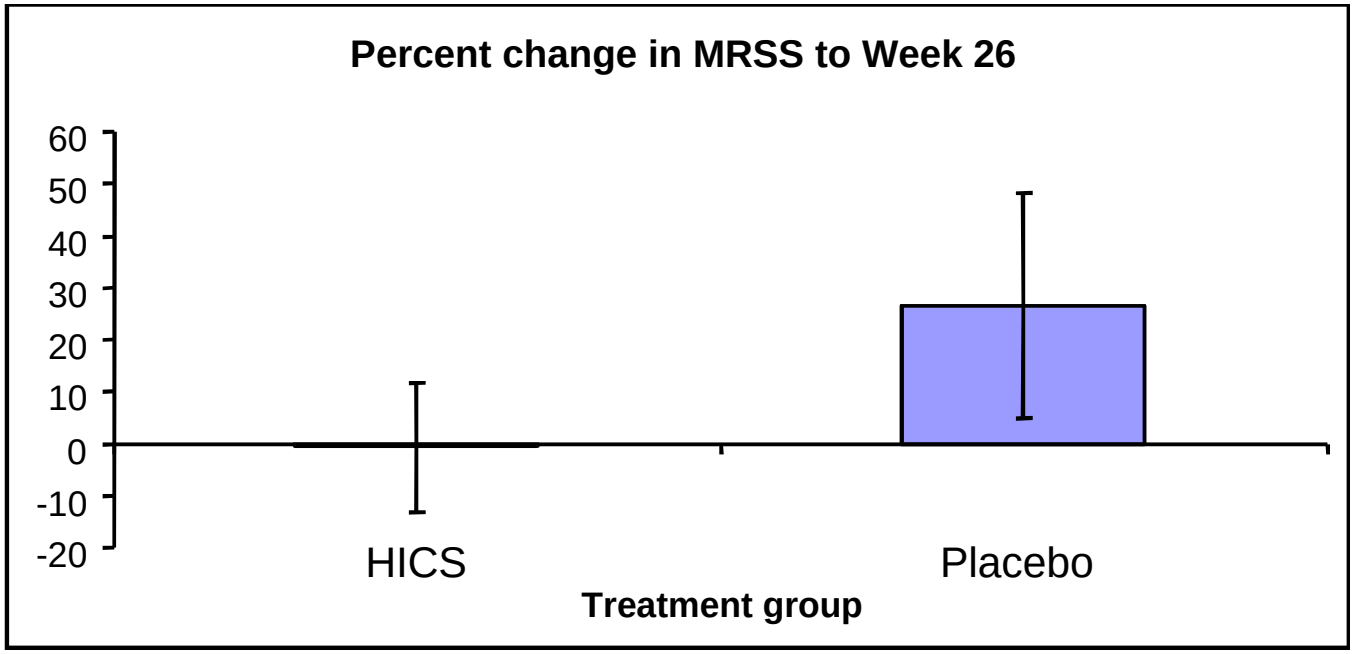
There were no safety concerns during the study at 26 and 52 weeks.

No SAE was judged treatment-related.

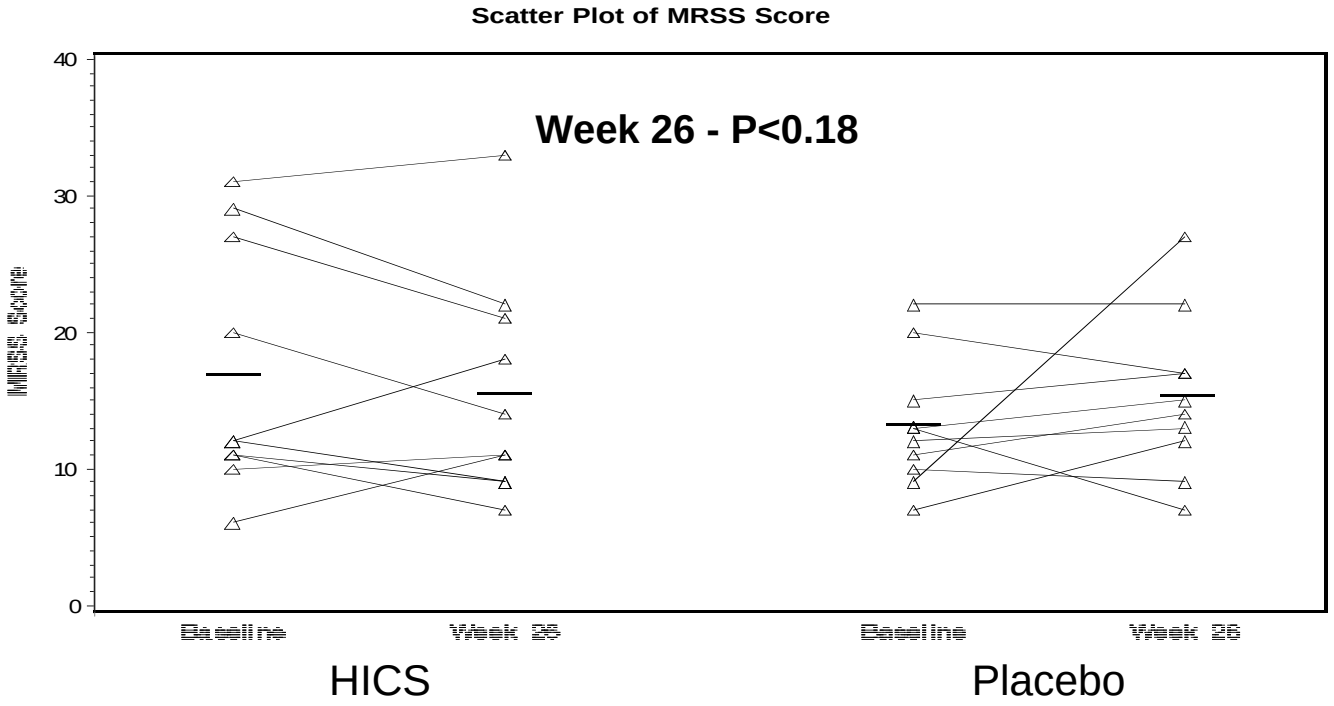
There was no deterioration in haematological, standard biochemical, thyroid function, cardiologic (LVEF, ECG, R-R, PAP) or pulmonary parameters measured in the study.

ELSDSS Trial Results - Primary Endpoints (II)

HICS exhibited a strong signal with the ability to arrest the deterioration in the MRSS when compared to placebo at **26 weeks** (in the order of 27.1%) - clinically significant (duration of illness dependent).

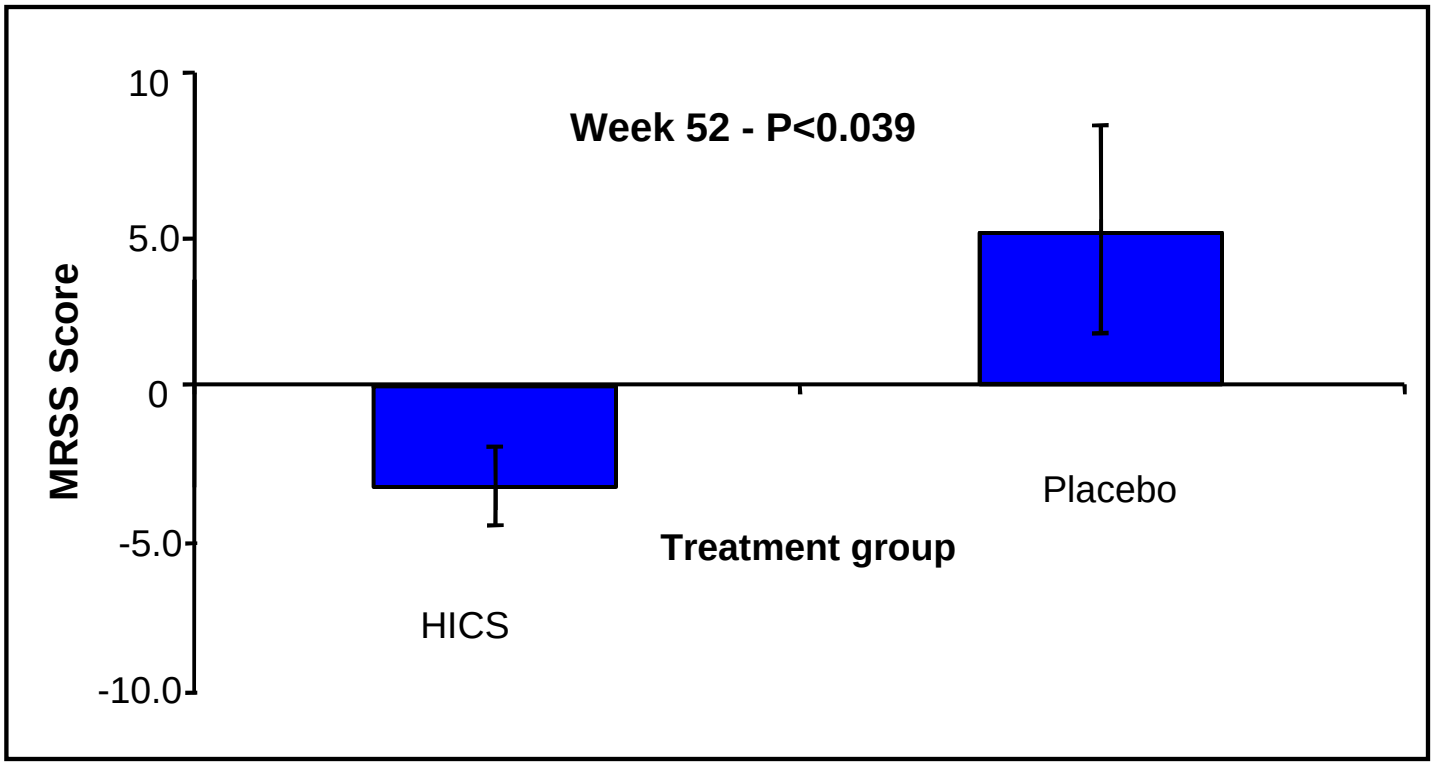


ELSDSS Trial Results - Primary Endpoints (III)



Clinically meaningful change in MRSS - >4 skin score units + >20% change from baseline. Mean skin score fell by 1.4±4.7 units with active treatment but worsened by 2.1±6.4 units on placebo (p=0.18, unpaired t-test). Responder analysis suggested **significant clinical improvement in MRSS** at 26 weeks occurred in 5 (50%) of actively treated patients compared with 1 (10%) in the control group.

ELSDSS Trial Results - Primary Endpoints (IV)



Statistically significant reduction in MRSS - >4 skin score units + >20% change from baseline. Mean skin score fell by 3.11±4.96 units with active treatment but worsened by 5.17±9.06 units on placebo (p<0.039, unpaired t-test). Responder analysis suggested **significant statistical and clinical improvement in MRSS at 52 weeks occurred in (70%) of actively treated patients** compared the control group.

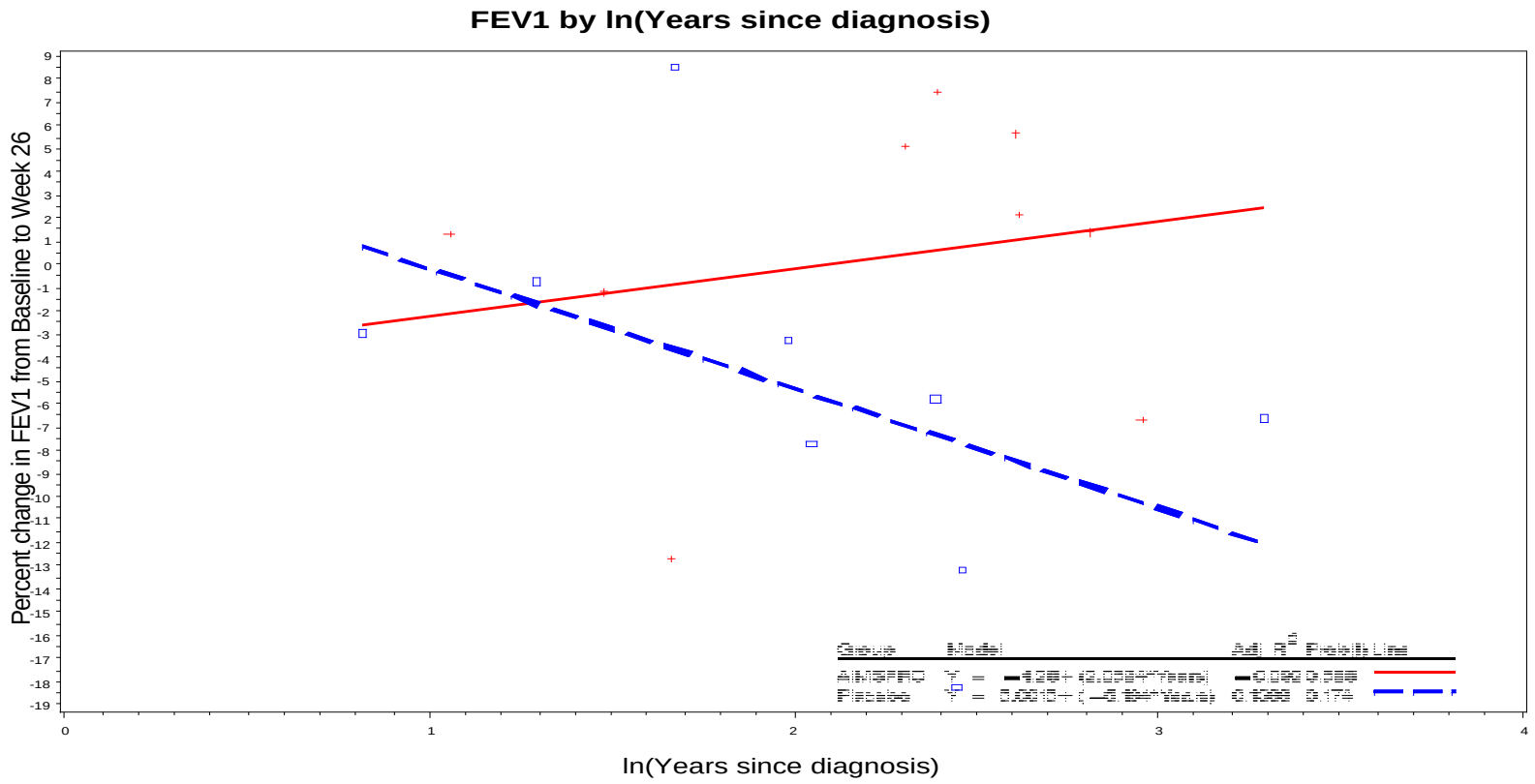
ELSDSS Trial Results - Secondary Endpoints (II)

Pulmonary Function Testing

HICS exhibited a near statistically significant increase in both the FEV1 and FVC compared to the placebo group at 26 weeks, thereby rescuing in effect the deterioration in lung function.

Importantly no change in TLC or DLCO were noted.

ELSDSS Trial Results - Secondary Endpoints (FEV1)



The FEV1 was observed to decrease in the Placebo group as compared to baseline at 26 weeks (-5.6%, p= 0.058) to a near significant degree, with no such deterioration being observed in the HICS treated group, where the FEV1 showed a marginal increase from baseline at 26 weeks (+0.27%, p=0.9039).

ELSDSS Trial Results - Secondary Endpoints (SF-36)

The SF-36 scores in general showed a strong signal with improvement of all eight of the individual scores assessed. The average increase was in the order of 41.6%. The difference in the overall SF-36 score was statistically significant between the HICS and Placebo treated groups at 26 weeks *(mean difference = 41.61%, p<0.04)*.

Summary of SF-36

Physical Function (overall difference + 20.05%, p=0.650)
HICS = +19.57%, Placebo = -0.480%

Role-Physical (overall difference + 89.26%, p=0.1961)
HICS = +60.71%, Placebo = -28.55%

Bodily Pain (overall difference + 35.65%, p=0.1880)
HICS = +12.53%, Placebo = -23.12%

General Health (overall difference +33.32%, p=0.444)
HICS = +22.10%, Placebo = -11.22%

Vitality (overall difference +29.3%, p=0.384)
HICS = +22.52%, Placebo = -6.77%

Social Functioning (overall difference +42.13%)
HICS = +14.58%, Placebo = -27.55%

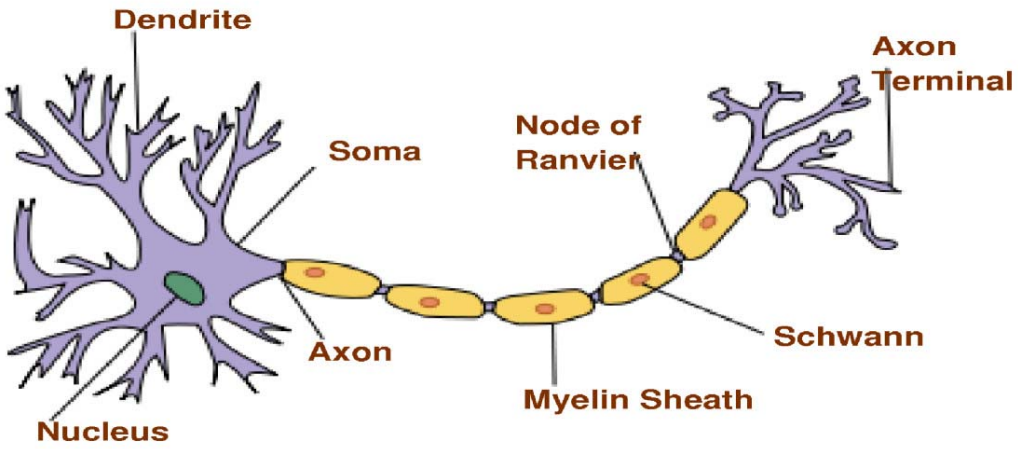
Role Emotional (overall difference +74.25%, p=0.356)
HICS = +71.47%, Placebo = -2.78%

Mental Health (overall difference +8.91%, p=0.583)
HICS = +8.62%, Placebo = -0.29%

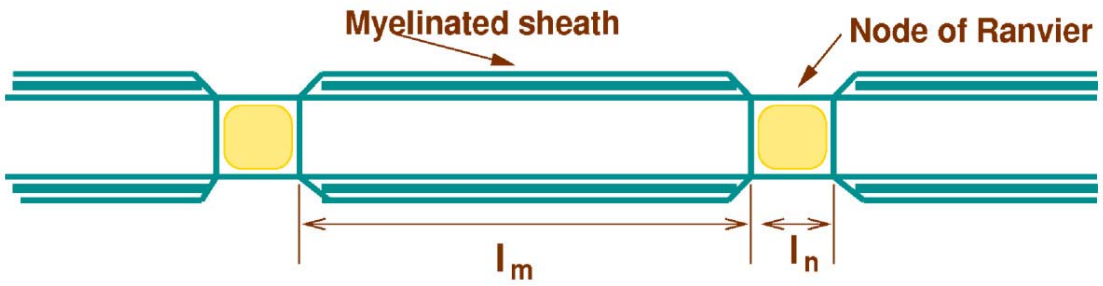
Summary of biomarker changes in ELSDSS Study

Biomarker parameter (6-weeks)	Implications of change
Inhibition of IL-1α	Anti-inflammatory
Reduction in IL-23	Confers resistance to autoimmune inflammatory response (Th17)
Reduction in TARC	Reduced Th2 chemotaxis Reduced pitting scars, ATA
Reduction in PDGF-BB	Reduced fibrogenesis Reduced pitting scars, ATA
Biomarker parameter (26-weeks)	**Implications of change**
Reduction in MCP-1	Anti-inflammatory effect
Increase in VEGF	Angiogenesis
Increase in b-FGF	Remodelling of ECM
Increase in IL-12p70	Confers resistance to autoimmune inflammatory response (in vivo)
Increase in PIIINP	Degradation products of remodelling
Reduction in COMP	Correlates with a reduction in MRSS
Reduction in TIMP2	Angiogenesis and repair
Reduction in MCP-2	Anti-inflammatory

The Myelin Sheath

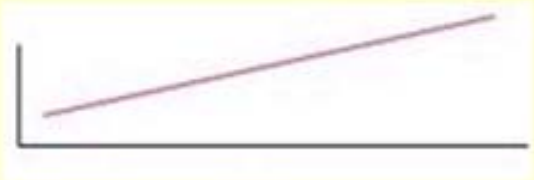


(a)

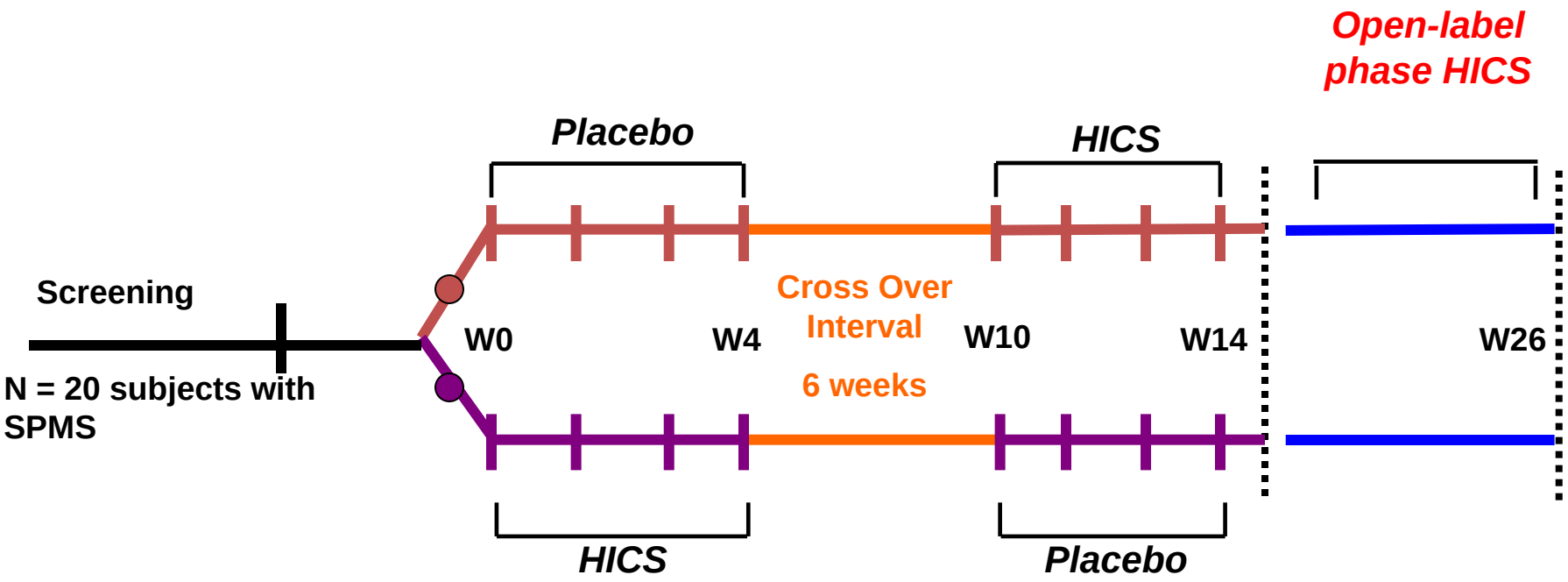


(b)

Types of Multiple Sclerosis

MS Type	Disease Progression	%of MS population
Relapsing-remitting (RR)		~85-90% of initial course. Characterized by unpredictable relapses followed by periods of months to years of relative quiet.
Secondary progressive		~65% of those with RR initially that begin to have neurologic decline between acute attacks without any definite periods of remission
Primary progressive		~10% who never have remission after their initial attack/MS symptoms. Characterized by progression of disability from onset, with no, or only occasional & minor, remissions/improvement
Progressive relapsing		~<5% at onset have a steady neurologic decline & also suffer clear superimposed attacks

SPMS Trial Design & Treatment Schedule



Groups

Group 1: Placebo
Group 2: 4.5mg/ml HICS 2 x week

Phase II Clinical Trial - Bladder Dysfunction in Secondary Progressive Multiple Sclerosis

Primary Endpoint Measures
Change in average voided volume [Time Frame: At 0, 4, 10 and 14 weeks]

Secondary Endpoint Measures
Change in average 24-hour frequency [Time Frame: At 0, 4, 10 and 14 weeks]

Change in visual acuity and colour vision [Time Frame: At 0, 4, 10 and 14 weeks]
Employs logMAR based and Farnsworth-Munsell 100 Hue testing.

Change in average 24-hour incontinence [Time Frame: At 0, 4, 10 and 14 weeks]

Change in urgency score [Time Frame: At 0, 4, 10 and 14 weeks]

Change in I-QOL score [Time Frame: At 0, 4, 10 and 14 weeks]

Change in Whittington Urgency Score [Time Frame: At 0, 4, 10 and 14 weeks]

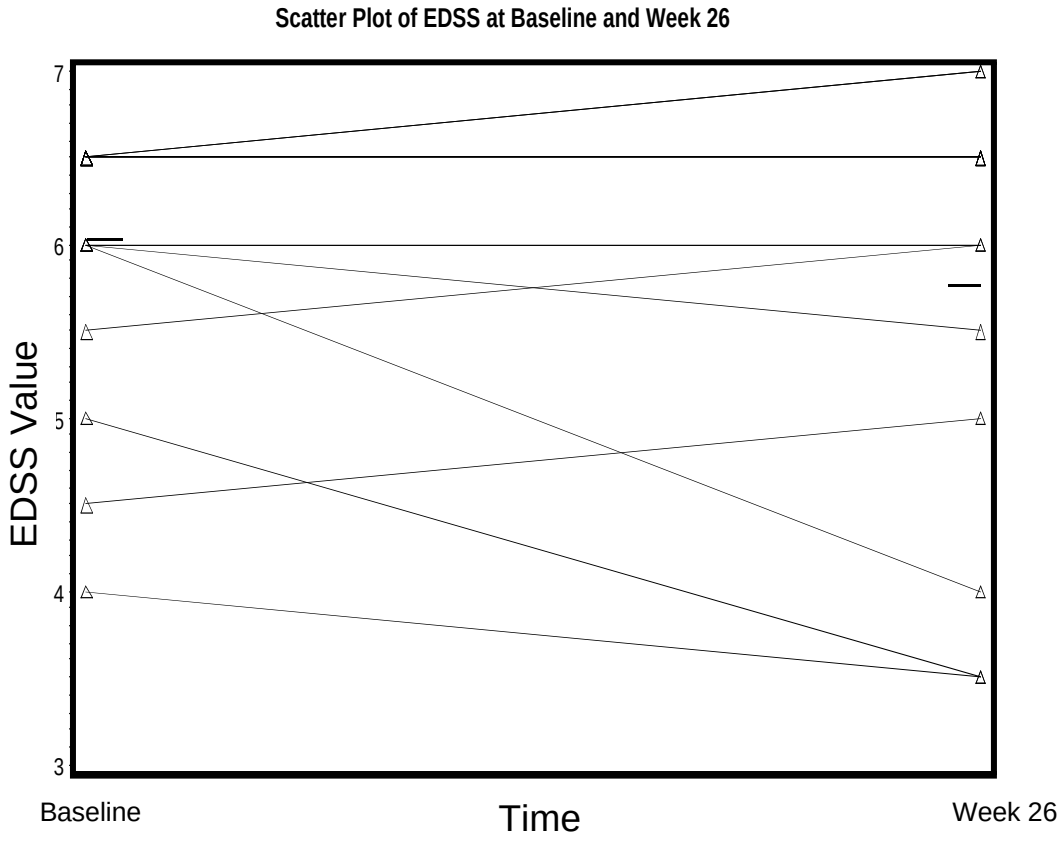
Change in Kurtzke EDS [Time Frame: At 0, 4, 10 and 14 weeks]

Change in MSIS-29 [Time Frame: At 0, 4, 10 and 14 weeks]

Change in MS FC [Time Frame: At 0, 4, 10 and 14 weeks]

Change in MS WS [Time Frame: At 0, 4, 10 and 14 weeks]

SPMS Trial Results - Secondary Endpoints (EDSS) - Week 26



n=15

27 % of patients progressed over 6-months

73 % of patients showed arrest of disease or clinical improvement

46 % of patients showed no clinical deterioration in SPMS as defined by a change in EDSS score over 6-months

27% of patients showed a clinical improvement with a fall in EDSS of (**-1.125**±0.95).

Overall improvement in the treatment group following 16-weeks of HICS assessed over 26-weeks showed a fall in EDSS of (**-0.17**±0.5)

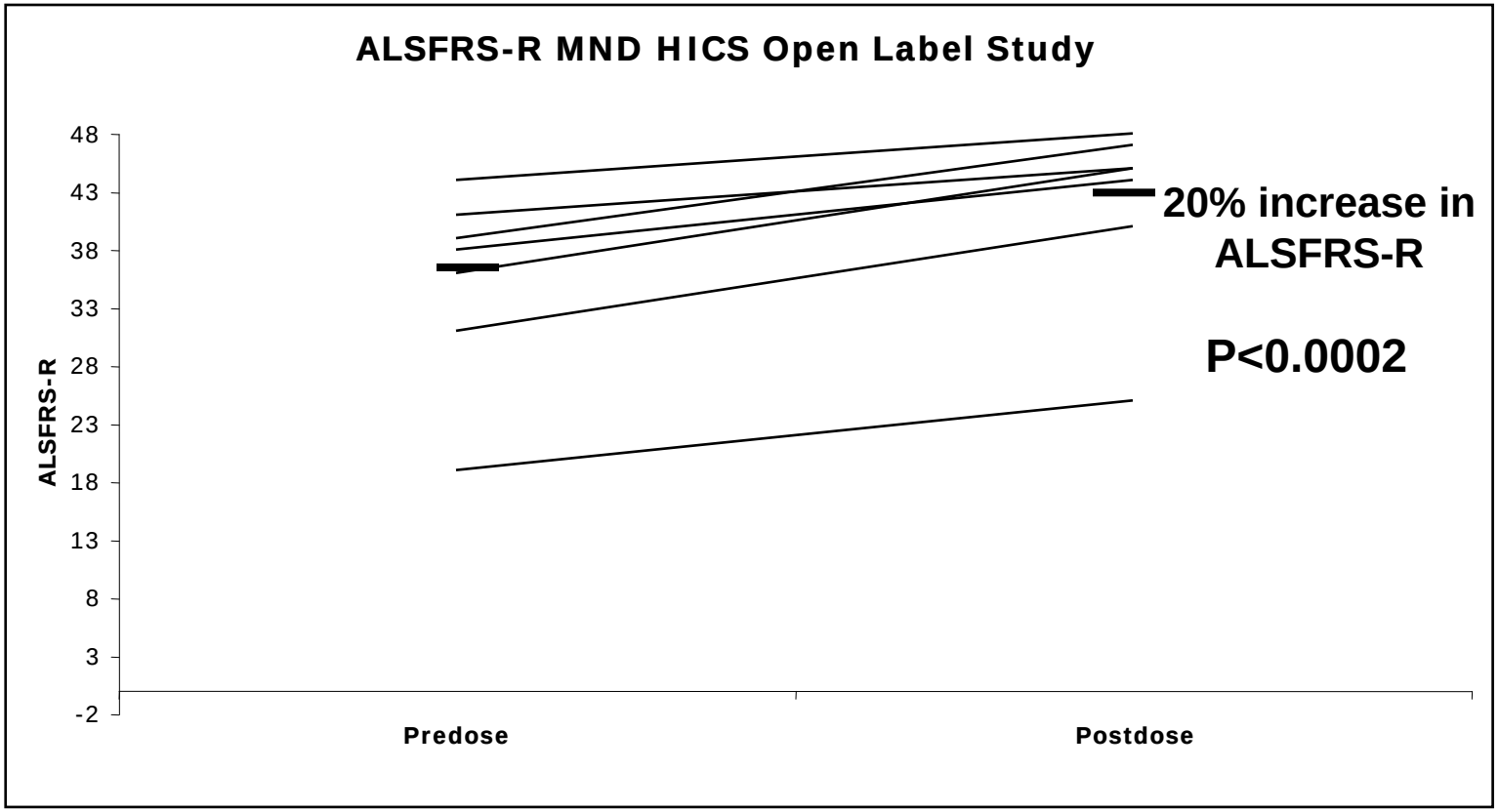
SPMS Trial Results – HICS versus Gilenya (fingolimod)

HICS –showed a **clinical improvement** with a **fall** in EDSS of (-1.125±0.95).
Overall improvement in the treatment group following 4-months of HICS assessed over 6-months showed a fall in EDSS of (-0.167±0.72) or over **52 weeks a fall of EDSS of (-0.313±0.8), responder rate 37.5%**.

Gilenya (Kappos, 2010) - in relapsing remitting and chronic progressive-relapsing MS patients, annualised relapse rate was 0.18 with 0.5 mg of fingolimod, 0.16 with 1.25 mg of fingolimod, and 0.40 with placebo.
The cumulative probability of disability progression was 17.7% with 0.5 mg of fingolimod, 16.6% with 1.25 mg of fingolimod, and 24.1% with placebo.

Those patients receiving 1.25mg of fingolimod showed a clinical improvement with a **fall in EDSS of (-0.03±0.88) in 108 weeks**.

Motor Neuron Disease (ALS) - FDA Orphan Drug Designation (HICS)



N = 7 Open-label study
Duration - 12-24 weeks
HICS 1ml (4.5mg/ml) daily treatment
Pre-dose ALSFRS-R = 35.4±3.14 (mean±SEM)
Post-dose ALSFRS-R = 42.0±2.99

Motor Neuron Disease (ALS) - FDA Orphan Drug Designation (HICS)

SUMMARY

8.1% increase in BMI

Maintenance of mid-thigh circumference

Maximal Voluntary Isometric Contraction (Strain Gauge) - increased by 35%

38.5% increase in ALSAQ-40

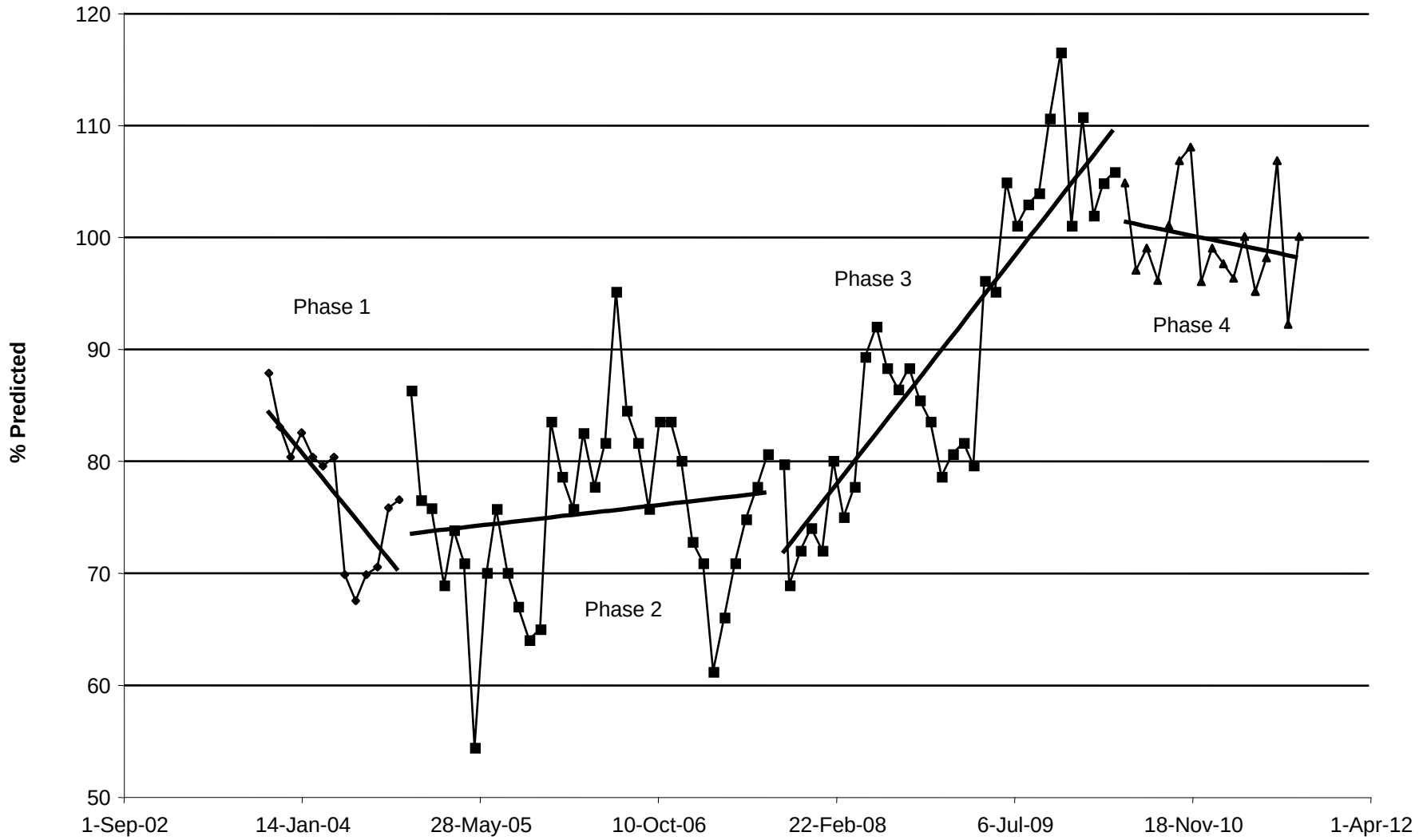
46.2% increase in ALS score of Jacblecki

Most rapid responses observed in symptoms including:

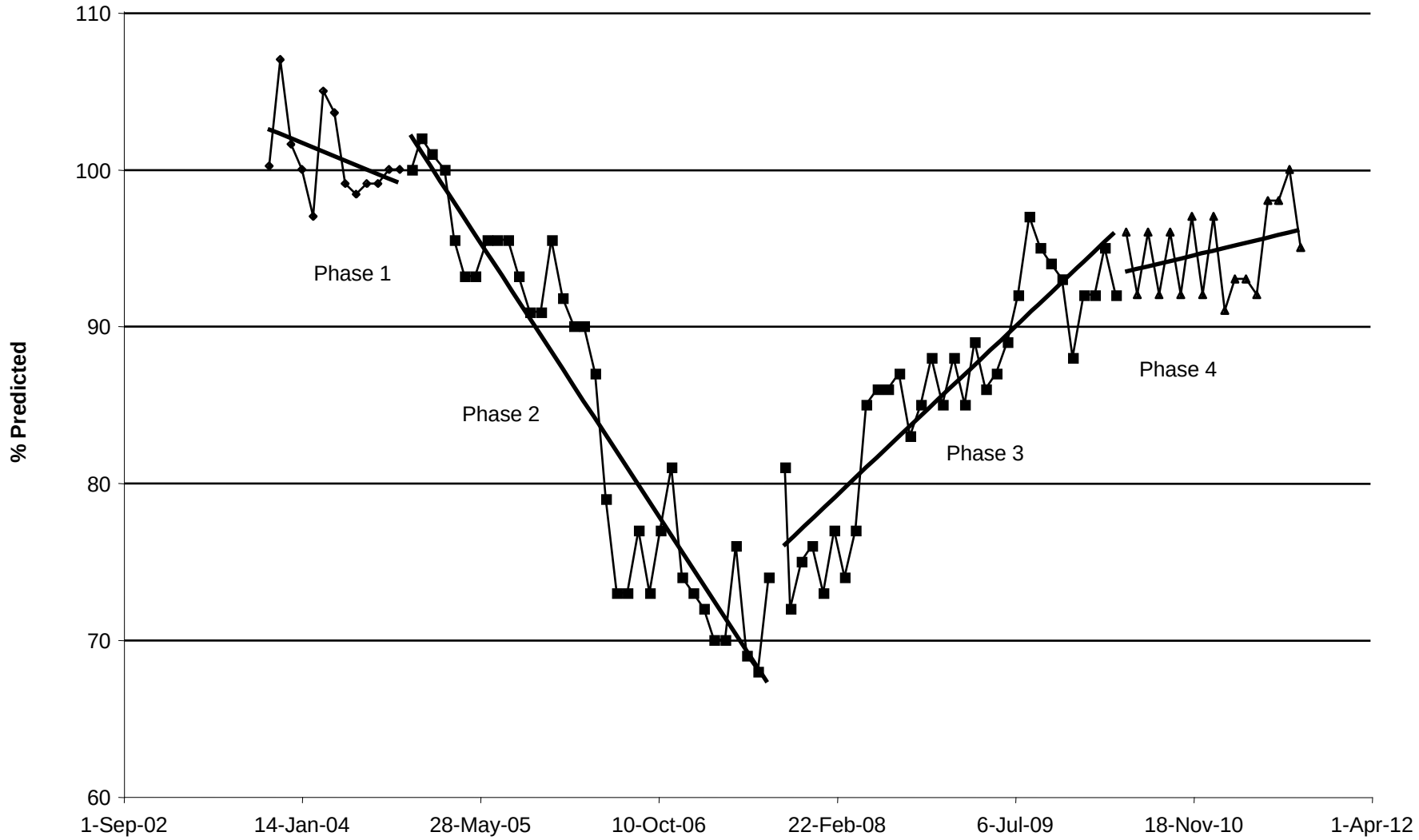
pseudobulbar and bulbar palsy
fasciculation
muscle spasms

Current study is ongoing investigating the MOA in SOD1 Tg(G93A)

Sniff nasal inspiratory pressure - 2002 to 2012



Forced vital capacity - 2002 to 2012



Observations in Named Patient/Compassionate Use Programme - MS Study

Results: Patient demographics and dosage.

N=140 patients with MS were treated with HICS.
Mean=age 47, range 25-68 yrs.

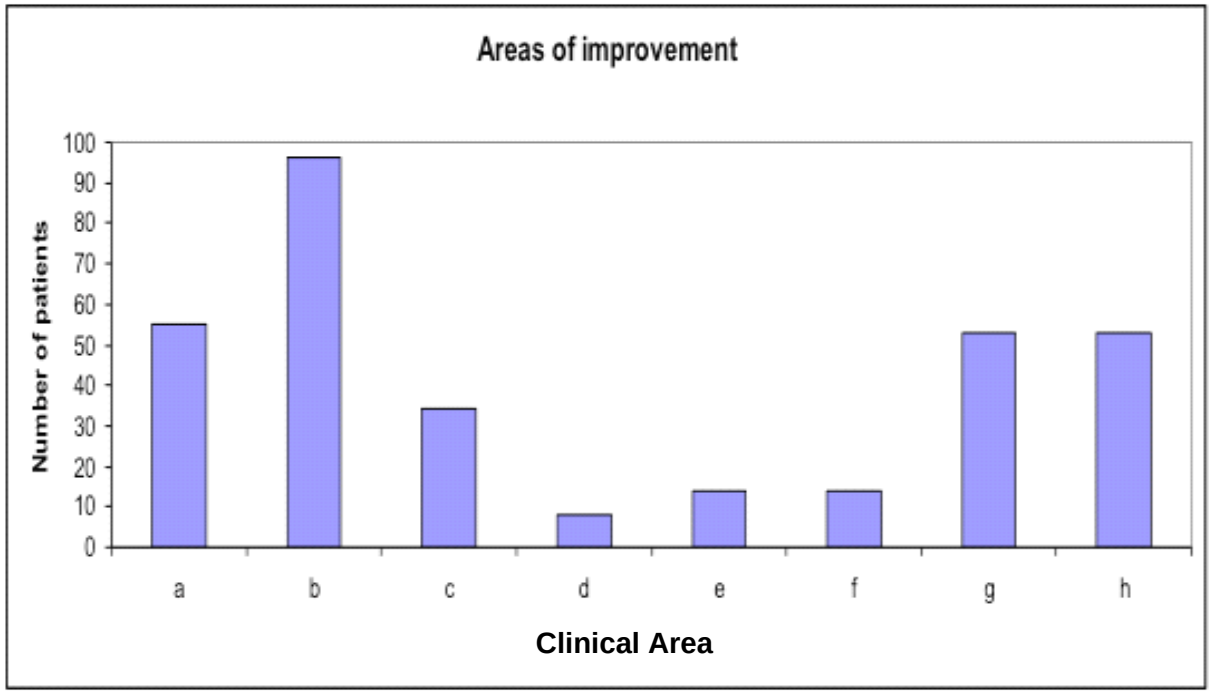
Dosage: 1 mL of HICS (4.5mg/mL) was administered subcutaneously.
dosing ranged from 4.5mg 2-3 times per week to 4.5mg every week or two. The most frequent dose used was 4.5mg twice weekly.

The duration of treatment ranged from 2 weeks to 3 years and equated to 3 to 150 doses of HICS at 4.5mg/mL.

The duration of the disease ranged from 3 months to 40 years (with a mean duration of disease of 13.6 years and a median 14 yrs.

Observations in Named Patient/Compassionate Use Programme - MS Study

The number of patients showing improvement in each clinical area (see earlier key - sensory, motor, bladder and energy most prominent)



68.7% responder rate in improvement in EDSS equivalent score (1= -0.25) ($p<0.005$)

Observations in Named Patient/Compassionate Use Programme - MS Study II

Clinical Observations not in trials B (multiple sclerosis) n=14
Recently, more detailed clinical scoring was used in the follow-up of 14 patients with a mean age of 53 years, (range 27-75), with mostly progressive MS. HICS doses of 4.5mg every **4 days** were prescribed for between 3 -31 months.

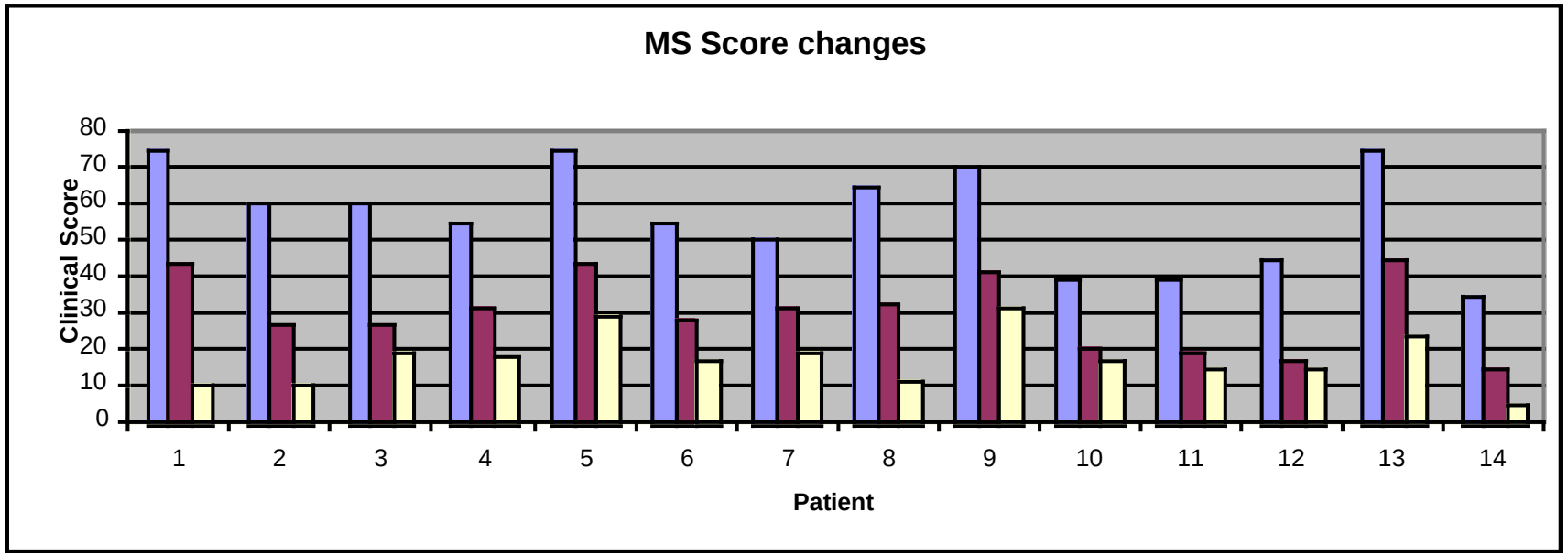
A more detailed clinical scoring system was used with +5 to -5 scoring in symptomatic clinical areas.

A maximum clinical score was calculated per patient based on the number of areas involved.

This gives a measure of the overall disease severity, in that when the clinical score nears the maximum score there is more severe disease involvement.

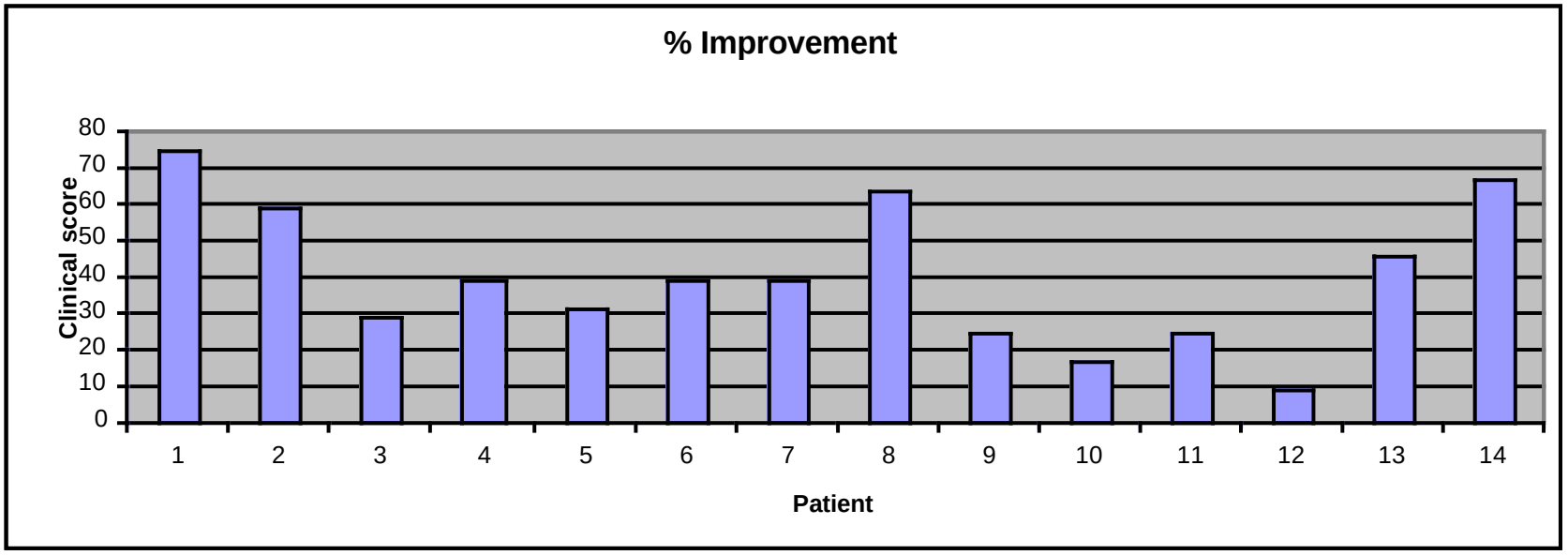
Observations in Named Patient/Compassionate Use Programme - MS Study II

Graph: shows three scores for each patient. Column 1 blue represents the maximum potential deficit given the number of clinical areas affected. Column 2 maroon and 3 yellow represent the patient's scores before and after treatment with HICS respectively. All patients show an improvement compared to baseline.



Observations in Named Patient/Compassionate Use Programme - MS Study II

Graph: shows the percentage improvement in each patient's individual improvement in clinical score from baseline after treatment with HICS (mean =39.1%, $p<0.001$)



Wellington Study: Anecdotal evidence of rapid improvement in colour vision in patients with multiple sclerosis

Study Group

6 patients: 2 M:4 F (optic disc pallor), age: 32-42 yrs

MS duration: 8-16 yrs, deteriorating in vision (no acute ON) over 3-14 yrs

Protocol

1ml subcutaneously initially once weekly then up to 3 times weekly according to neurological response.

Assessments - t=0, t=1h, t=7d, and t=28d-49d

No significant side effects were encountered

Measures

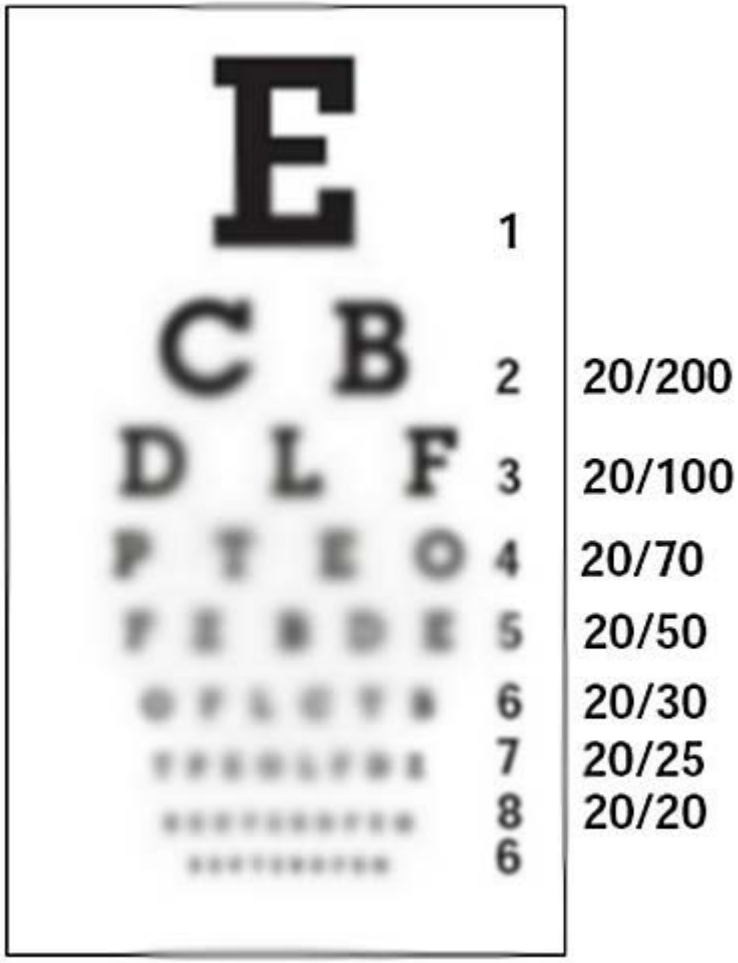
Corrected distance acuity

Farnsworth-Munsell 100-Hue test data (chromatic discrimination)

Monocular visual evoked potential studies

Wellington Study

Visual Acuity*

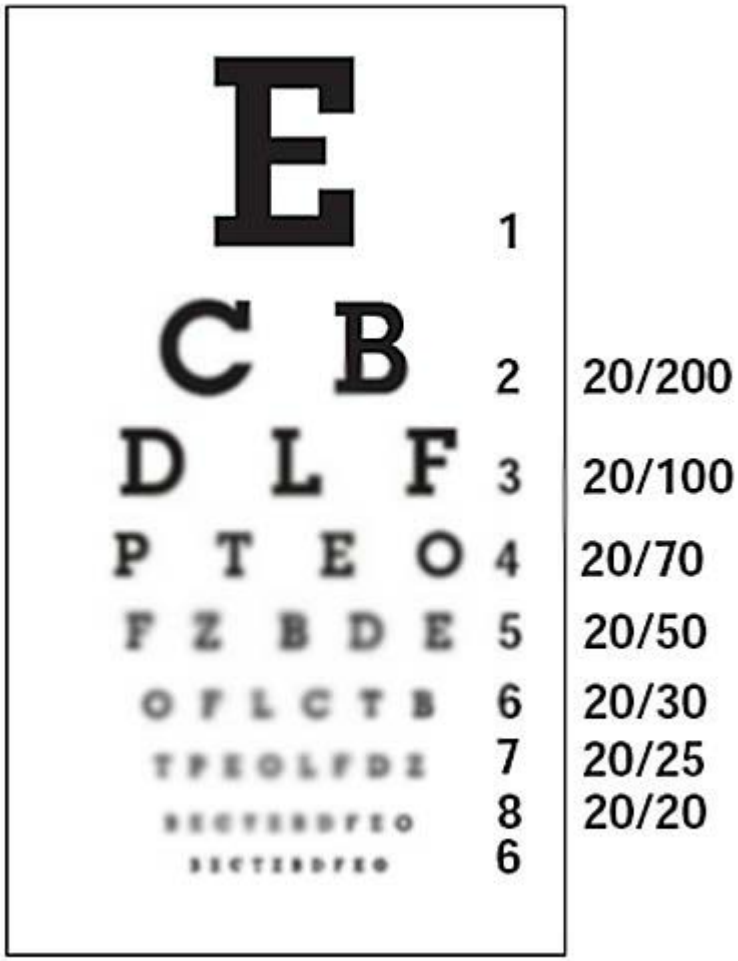


*1 Patient only

presentation analogy

Wellington Study

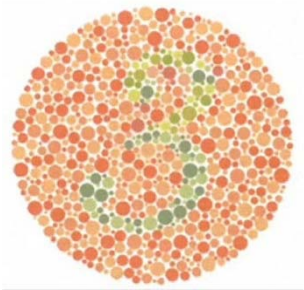
Visual Acuity*



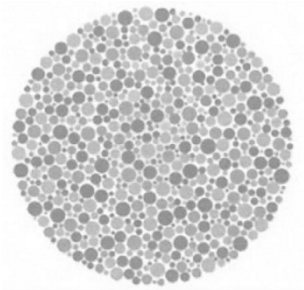
*1 Patient only

presentation analogy

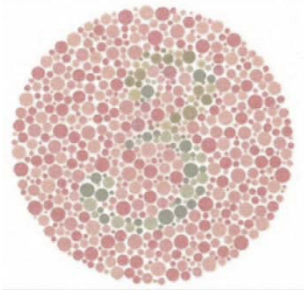
Wellington Study (Colour Perception)



100% - An individual with normal vision will see this when they look at an ISHIHARA chart plate



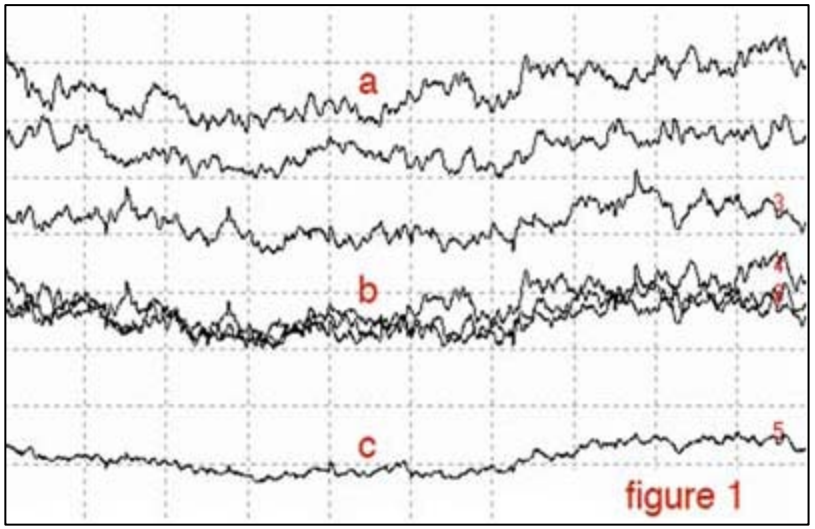
0% - Multiple Sclerosis patients often suffer loss of colour vision when their optic nerves become inflamed. They might typically see the same chart plate like this.



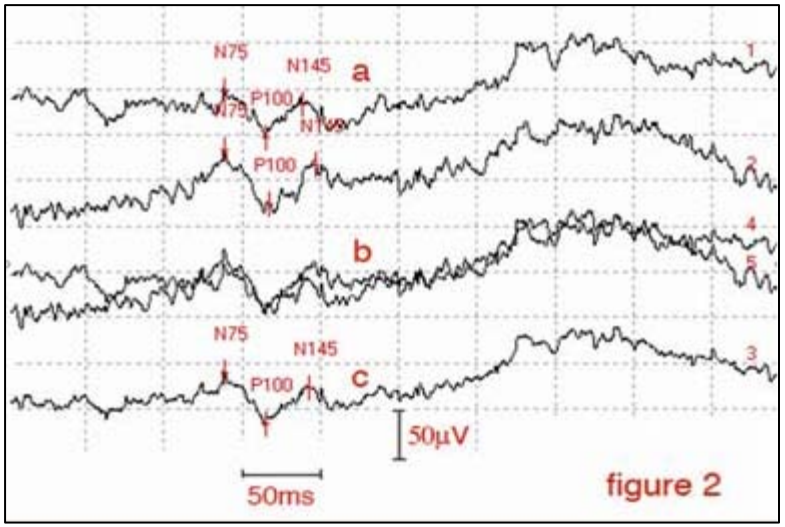
50% - Peer-reviewed work has confirmed that with HICS® Improvements to the level shown are possible.

Wellington Study (Visual Evoked Potentials)

Female patient with optic neuritis (MS)



Before injection



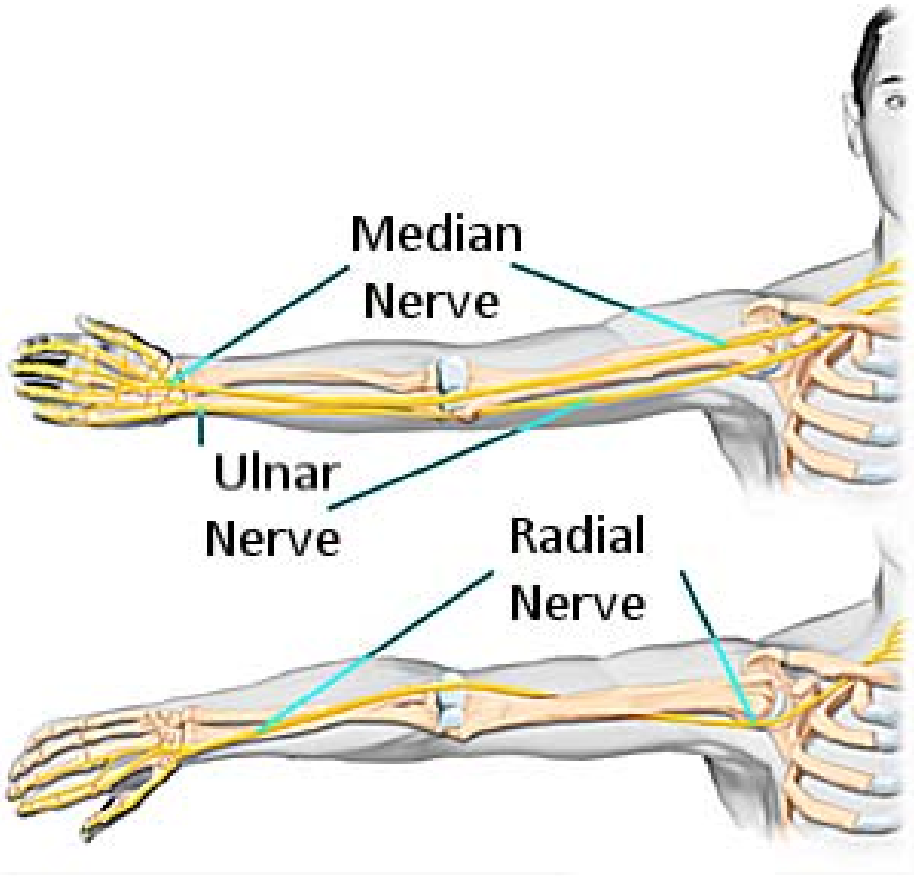
60 minutes post injection

Reversal of conduction block in optic nerve fibres

Nerve Conduction

Motor nerve function

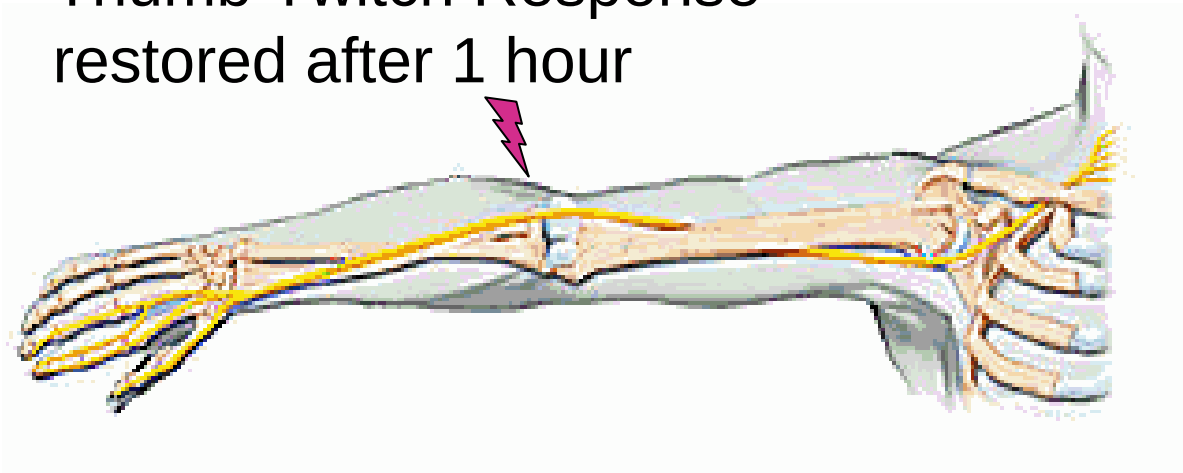
Individual patients



Conduction Security

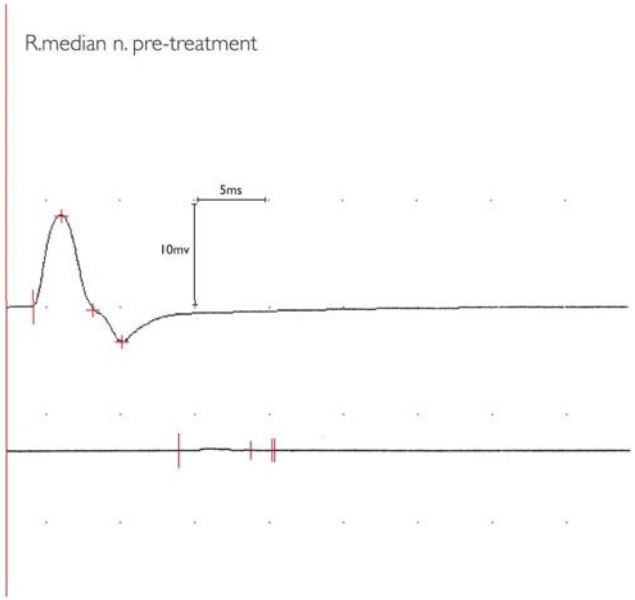
Post HICS® Injection

Thumb Twitch Response
restored after 1 hour



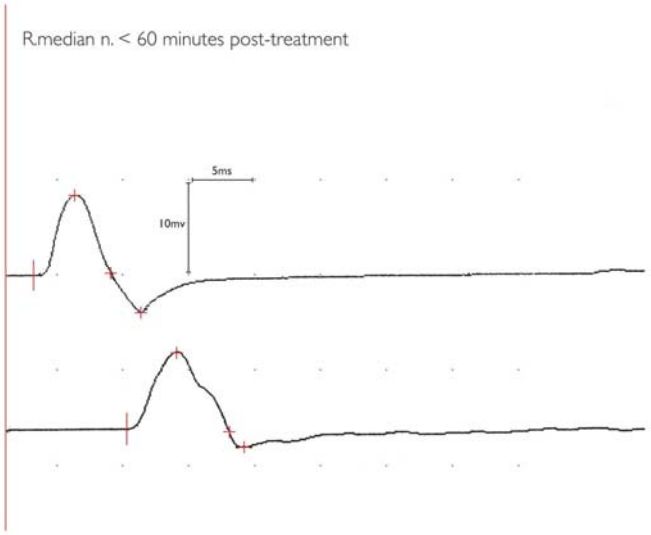
Motor Nerve Conduction Studies in CIDP (Radial nerve)

Pre-treatment



Focal inflammation produces demyelination
and motor fibre conduction block

Post-treatment



Reversal of motor nerve conduction block

Thank You

Video footage

http://www.youtube.com/watch?v=vqJQ5vdEJpc