A Phase II study demonstrating efficacy and safety of Mesenchymal Precursor Cells in low back pain due to disc degeneration

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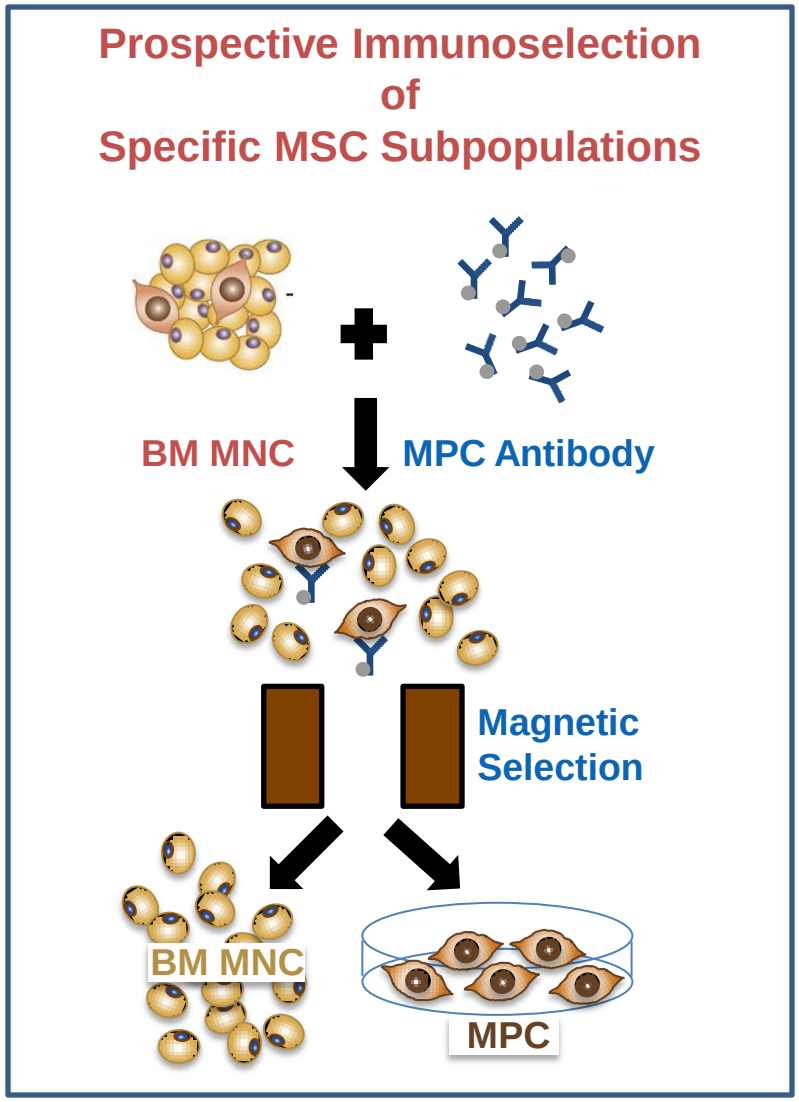
Gap In Non-Invasive Treatment Modalities For Chronic Low Back Pain Due To Degenerative Disc Disease (DDD)

- Over 4 million patients in the US have chronic back pain due to disc degeneration
- Current treatment options for chronic back pain involve either palliative measures or invasive surgery
  - Most episodes of LBP will recover within a few months, but some will develop chronic LBP (CLBP)
  - For patients with CLBP, conservative measures only mask the symptoms while doing nothing to fix the underlying pathology until the symptoms can no longer be managed and invasive surgery is the only option
  - Surgery is an invasive and expensive procedure to deal with CLBP
- A successful therapy for the treatment of CLBP due to DDD needs to provide a non-surgical, sustained (at least 6-12 months) and clinically significant improvement in pain and function with no further interventions
  - Between group mean differences less relevant in this population
  - Individual responder analysis for pain and function more relevant, as per consensus [1]
  - Similar bar for treatment success as for permanent surgical interventions (fusion, artificial disc)
  - Minimally Important Changes – at least 30% improvement in VAS and at least 10 point improvement in Oswestry Disability Index (ODI) [1] to be clinically relevant

[1] VIII International Forum on Primary Care Research on Low Back Pain (Amsterdam, June 2006) ; Ostelo et al Spine Vol 33,no1.pp90-94

Mesenchymal Precursor Cells (MPCs) for treatment of low back pain due to degenerated intervertebral discs

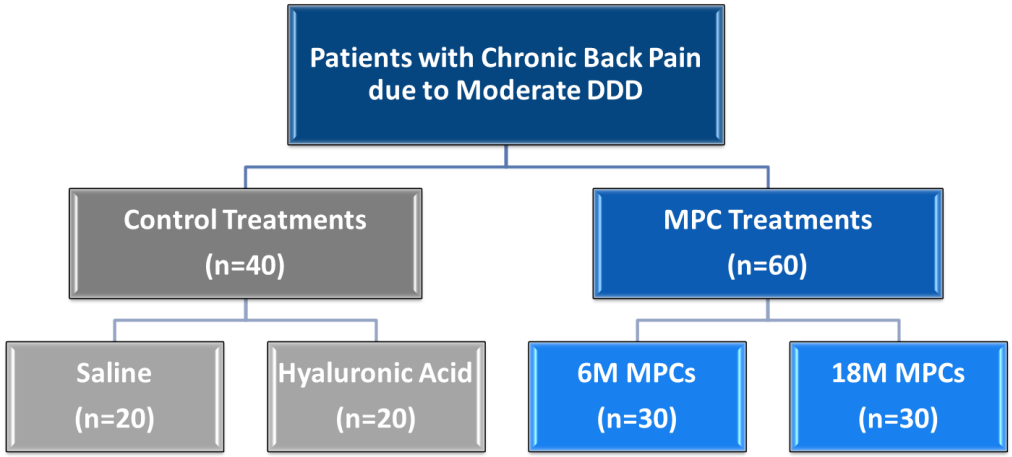


mesoblast

- Highly purified, immunoselected Stro-1/Stro-3 positive Mesenchymal Precursor Cells (MPCs)
  - Relatively homogeneous, well characterized cells
  - Increased *in vitro* differentiation efficiency into cells of the bone, fat and cartilage lineages
  - Not immunogenic and suppress immune responses
- Allogeneic MPC therapy offers "off the shelf" logistics
  - Defined product characterization
  - Established potency assays and release criteria
  - Batch-to-batch consistency
- MPCs secrete multiple factors in the appropriate concentration, sequence and duration in response to disease/injury-specific micro-environmental cues
  - Detect injury and inflammation
  - Respond to local stimuli and signals from the injured tissue
  - Release a wide range of biomolecules (growth factors, chemokines, enzymes etc.)
  - Increased proteoglycan synthesis
  - increased migration/proliferation of nucleus cells
- Demonstrated ability to repair the intervertebral disc in ovine preclinical model of disc degeneration[1]

[1] Ghosh et al. *J Neurosurg: Spine*, March 9, 2012

Study Design



- Prospective, multi-center, randomized, double-blind, controlled study
  - Patients and radiographic evaluators blinded to treatment
- Follow-up: 1, 3, 6, 12, 24 & 36 months
- Safety Evaluations
  - Adverse Events
  - Treatment Failure (Surgical & Injection Interventions)
  - Immunological Testing
  - Blood chemistry & inflammatory markers
  - Radiographic
    - Heterotopic ossification
    - Disc degeneration
- Efficacy Evaluations
  - Radiographic Changes
    - MRI
    - X-ray & Stability
  - Lower Back and Leg Pain measured by VAS Score
  - Oswestry Disability Index (ODI)
  - SF-36
  - Work Productivity & Activity Index (WPAI)
  - Medication usage

Patient Population

Inclusion Criteria

- Adult patients
- DDD with 1 symptomatic level from L1 to S1 with back pain >6 months
- Failed 3 Months Non-Operative Care
- Patients with a modified Pfirrmann score of 3, 4, 5 or 6
- With or without contained disc herniation up to a 3mm protrusion with no radiographic evidence of neurological compression.
- Disc height loss of <30% compared to a normal adjacent disc based upon radiographic evaluation
- VAS Back pain >40
- ODI Score >30

Exclusion Criteria

- Clinically significant nerve or sacroiliac joint pain.
- Clinically significant facet pain as determined by a diagnostic medial branch block or facet joint injection
- Symptomatic involvement of more than one lumbar disc level.
- Intact disc bulge/protrusion or focal herniation at the symptomatic level(s) > 3 mm or presence of disc extrusion or sequestration
- Discs with full thickness tears with free flowing contrast through the annulus fibrosis
- Lumbar intervertebral foraminal stenosis at the affected level(s) resulting in clinically significant spinal nerve root compression.

Demographics & Baseline Characteristics

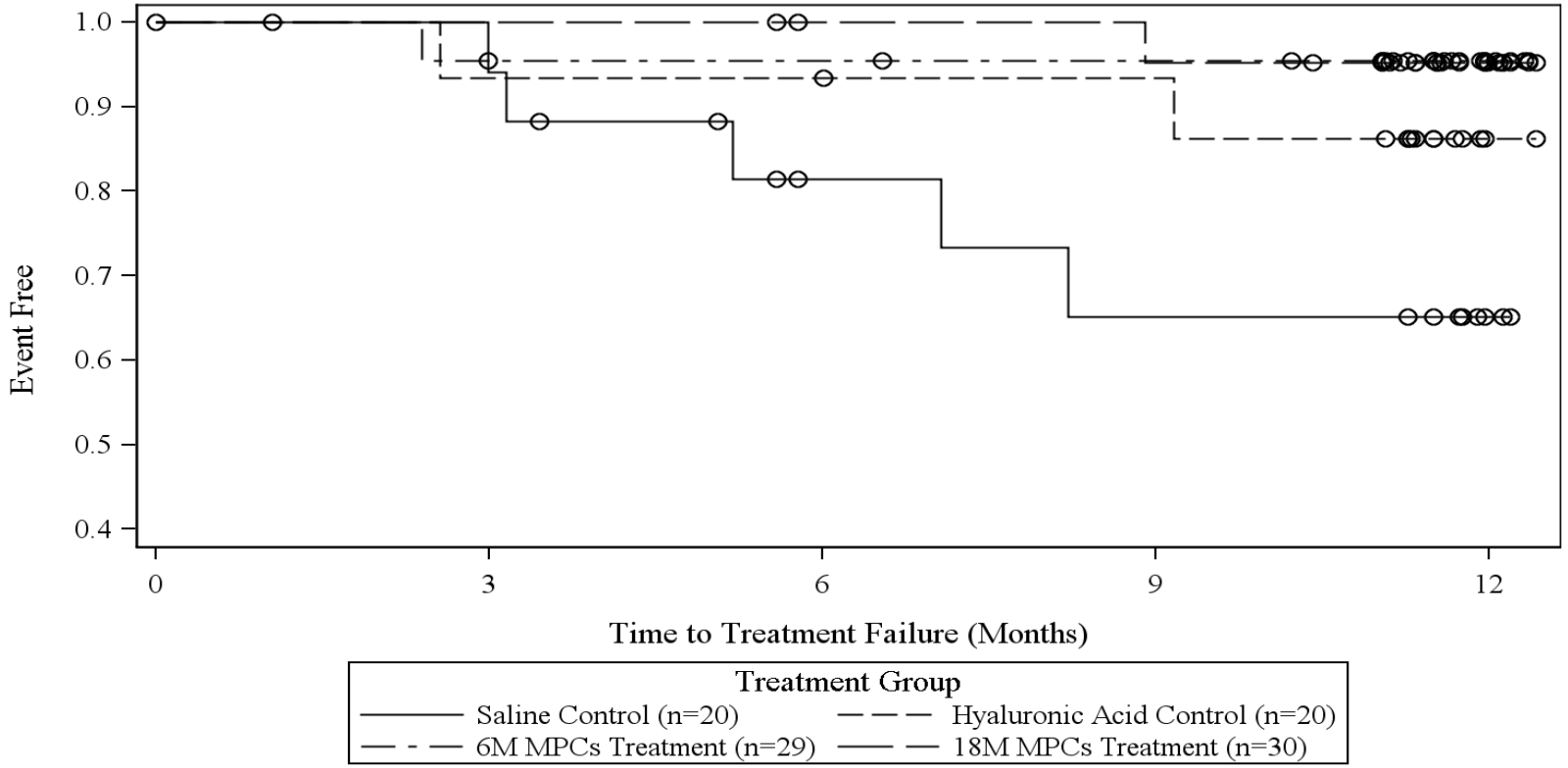
	Saline	HA	6M MPCs	18M MPCs	p-value
Sex					0.122
Male, %	50.0	50.0	40.0	70.0	
Female, %	50.0	50.0	60.0	30.0	
Age, mean	44.5	40.3	45.1	37.9	0.056
Weight, mean kg	70.46	79.87	77.51	84.53	0.024
Duration DDD, mean years	5.9	5.0	8.4	3.7	0.009
Duration Low Back Pain, mean years	7.9	7.6	9.9	7.4	0.443
VAS Low Back, mean mm (1-100)	66.9	71.9	69.7	71.5	0.650
ODI, mean (1-100)	44.40	46.80	52.06	50.68	0.234
Modified Pfirrman Score (1-8)[1]					0.570
Grade I - V, %	80.0	90.0	83.3	96.7	
Grade VI - VIII, %	20.0	10.0	16.7	3.3	

[1] Baseline score of blinded independent radiologist. Modified Pfirrmann score for inclusion in the study determined by investigators.

Safety Results

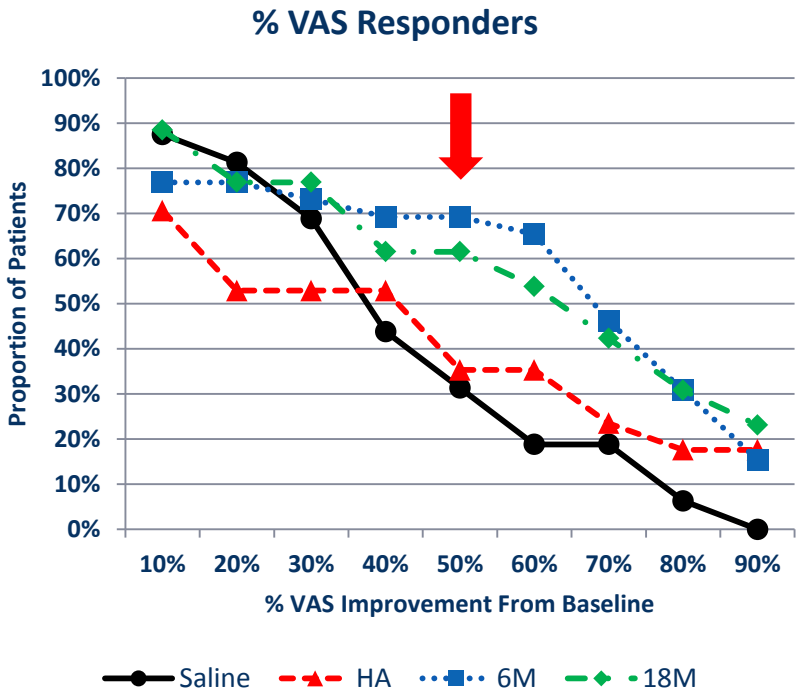
- Procedure and treatment well tolerated
- No significant differences in SAEs or AEs across all 4 groups
- No clinical symptoms of allergic or immune reaction to allogeneic MPCs
- The only AE reported in >10% of patients was back pain, new different or worsening
  - Overall back pain was reported in 40.0% of Saline, 20.0% of HA, 26.7% of 6M and 50.0% of 18M patients
  - The high dose had an increased incidence of early post-injection reports of back pain (within 7 days of treatment injection) compared to the other groups

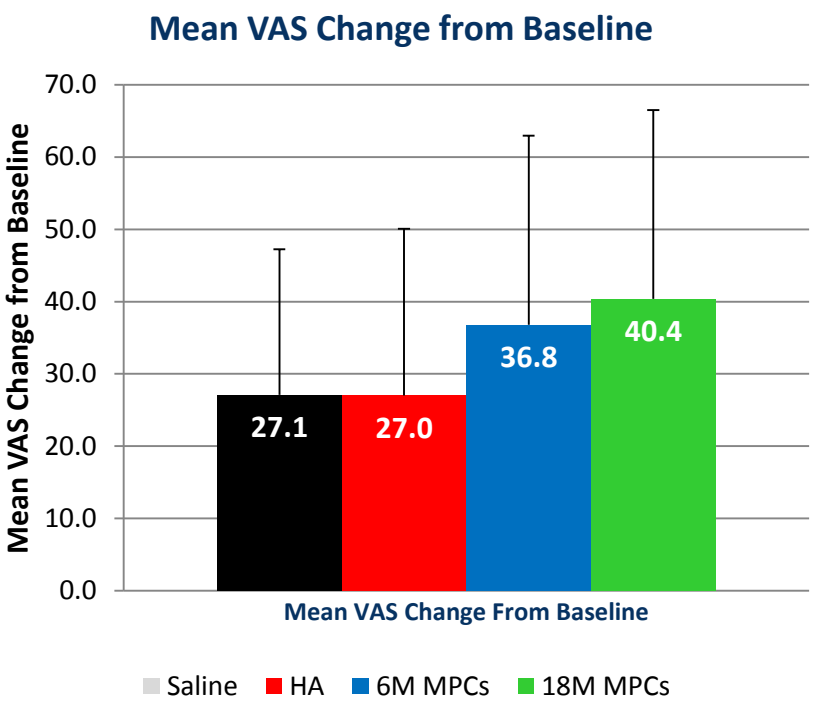
MPC treated groups had significantly reduced time to intervention at the treated level compared to saline controls



- Interventions occurred in 25.0% Saline, 10.0% HA, 6.9% 6M and 3.3% 18M groups
- The 6M and 18M groups had a statistically lower rate of intervention compared to the saline group. Overall log rank p=0.024 (p=0.024 & p=0.010)
- Treatment Failure: surgical interventions (e.g. fusion surgery, discectomy, artificial disc replacement) and injections (epidural steroids, rhizotomy and transforaminal injections) at the treated level

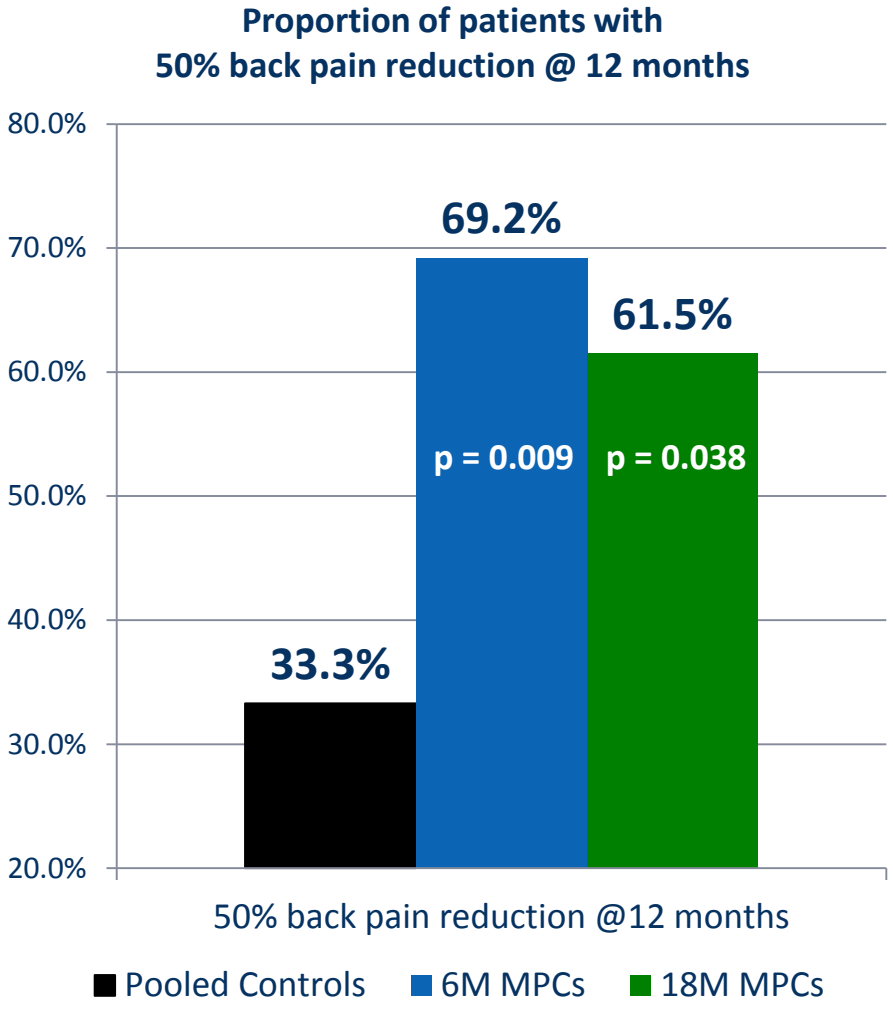
MPC treated groups had greater reduction in pain than controls at 12 months, as measured by responder analysis or mean change from baseline

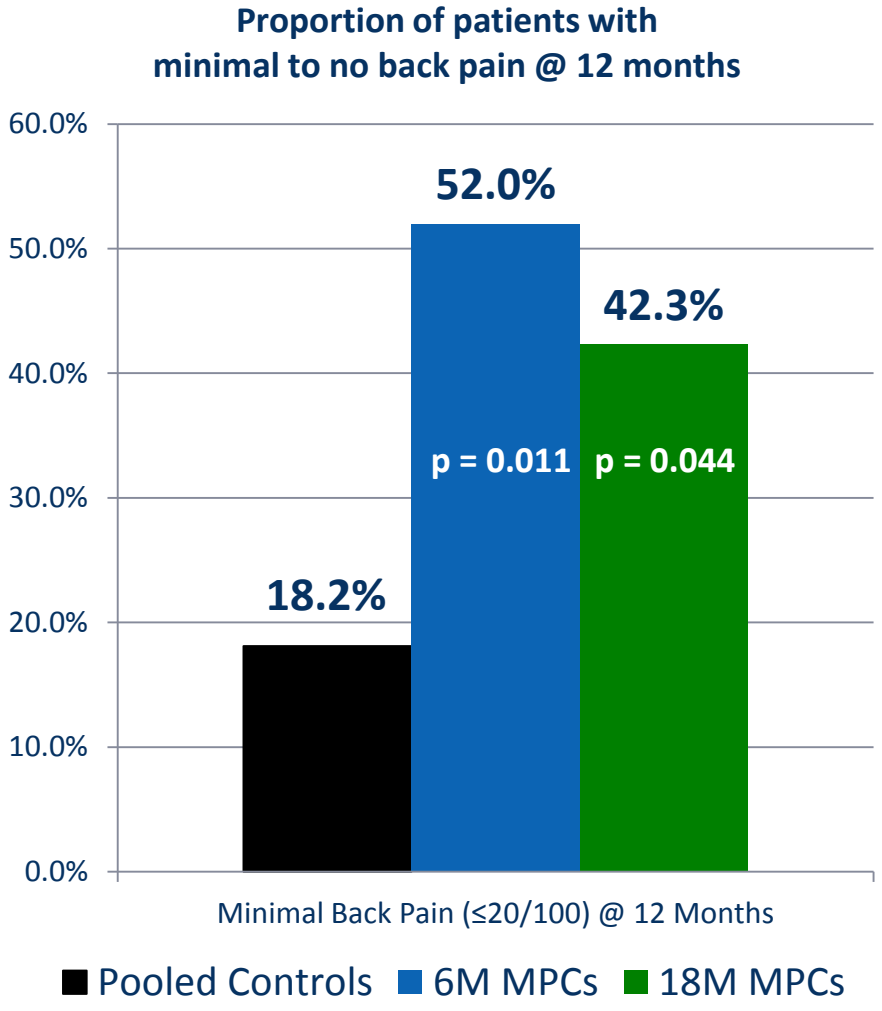




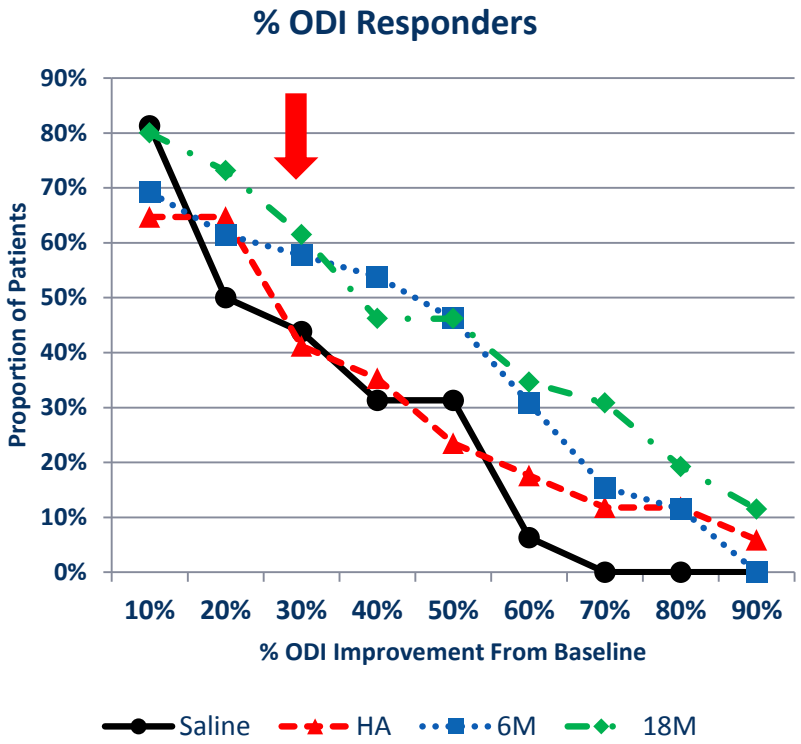
- 6M and 18M MPCs treated groups performed similarly and the saline and HA control groups performed similarly
- The 6M MPC group had 69.2%, the 18M MPC group had 61.5% of patients achieving at least 50% reduction in VAS back pain while the Saline group had only 31.3% and the HA group had 35. 3% (p = 0.036)
- Mean reduction from baseline in the VAS low back pain was 40.4 for 18M group, 36.8 for 6M group, 27.0 for pooled controls (p=0.11 for 6M vs. pooled control and p=0.046 for 18M vs. pooled control)
- Large differences around the mean reflect responder vs. non-responder outcomes

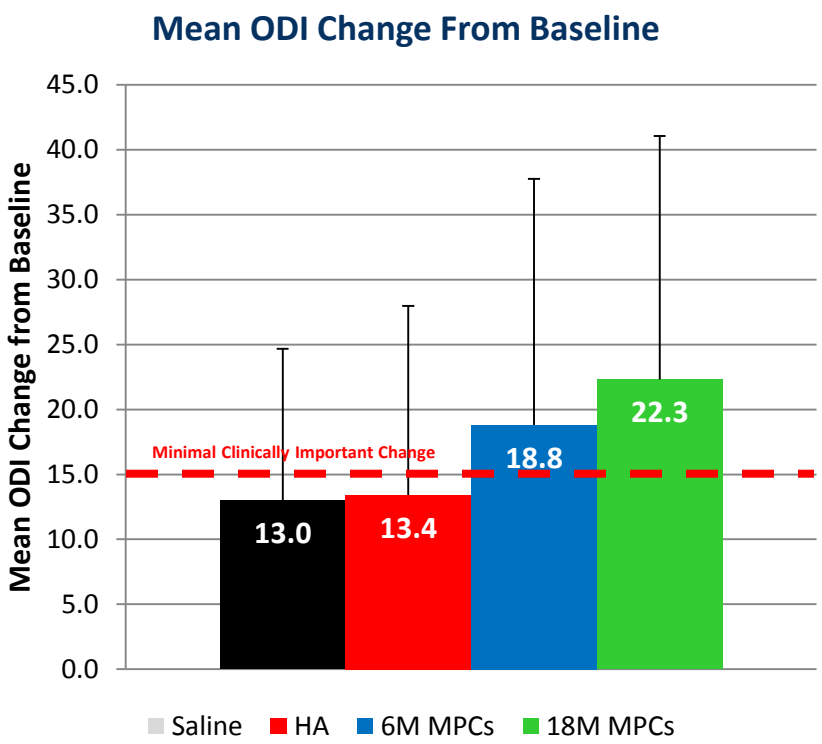
MPC groups have a greater proportion of patients with at least a 50% improvement in back pain or minimal/no residual back pain at 12 months relative to controls





MPCs demonstrate improvement in function compared to controls at 12 months in responders or mean change





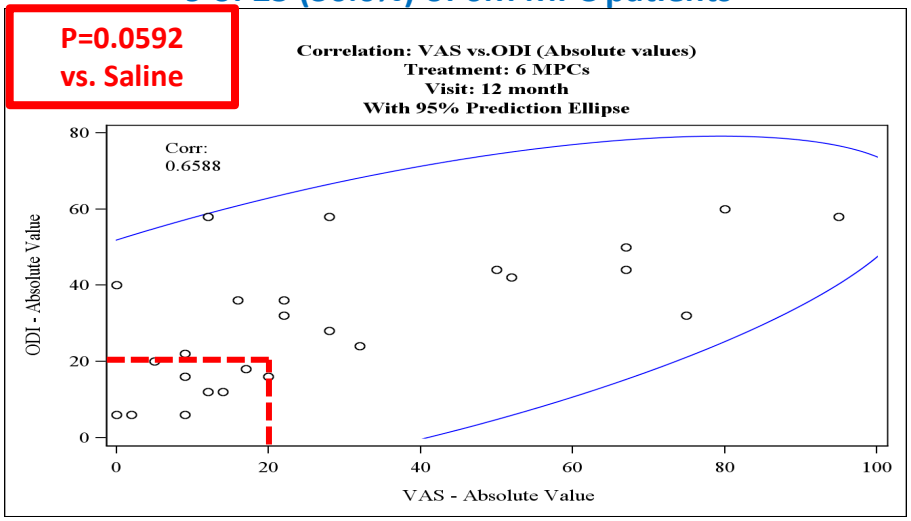
- 6M (57.7%) and 18M (61.5%) had a greater % of patients with a minimally important clinical difference (MCID) ≥30% reduction in ODI compared to Saline (43.8%) & HA (41.2%) at 12 months
- 6M (46.2%) and 18M (46.2%) had a greater % of patients with ≥50% reduction in ODI compared to Saline (31.3%) & HA (23.5.%) at 12 months

- Mean reduction from baseline in the ODI was 43% for 18M group, 35% for 6M group, 30% for HA and 28% for saline (p=0.09 for 18M vs. saline)
- Mean ODI change from baseline exceeds the FDA accepted Minimal Clinically Important Difference (MCID) for the MPC treated groups, but does not exceed it for the MPC control groups
- Large differences around the mean reflect responder vs. non-responder outcomes

MPC treated groups had a nearly five fold greater proportion of patients at 12 months with minimal/no residual pain AND minimal/no functional disability relative to saline controls

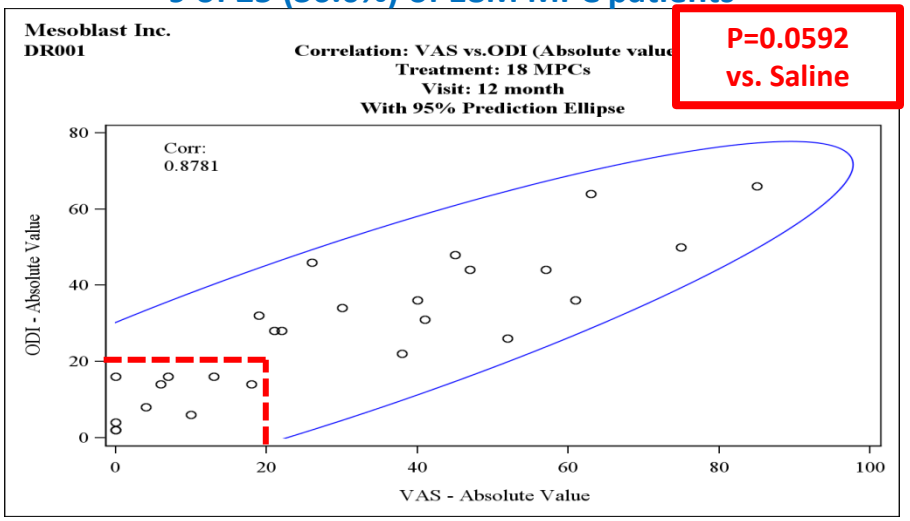
9 of 25 (36.0%) of 6M MPC patients

P=0.0592 vs. Saline

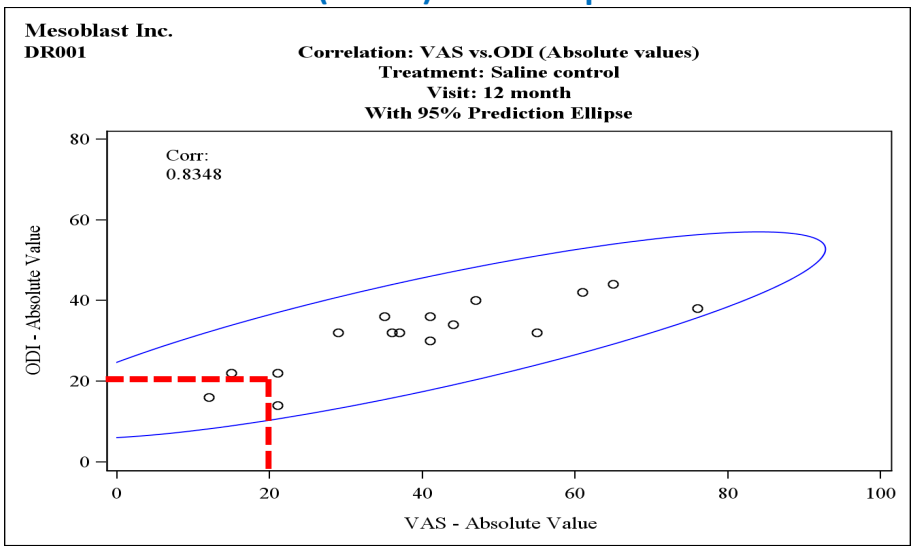


9 of 25 (36.0%) of 18M MPC patients

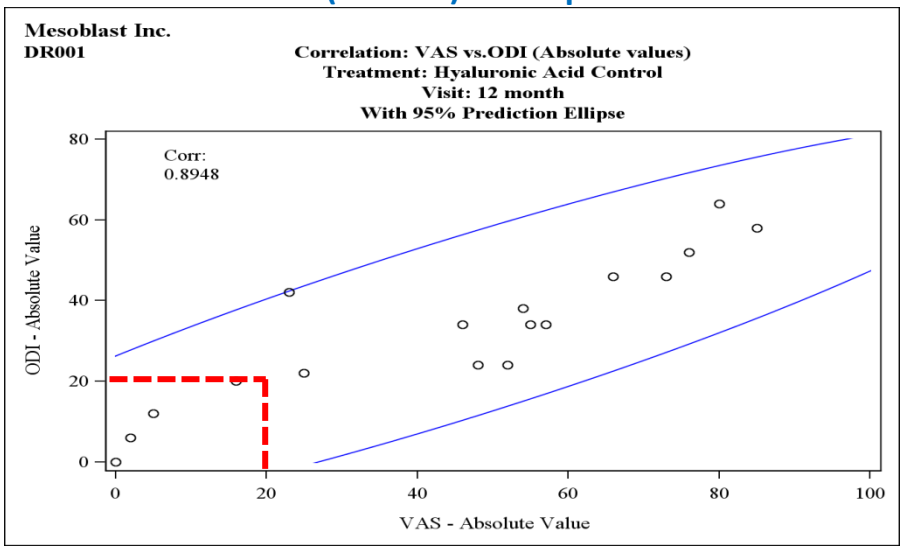
P=0.0592 vs. Saline



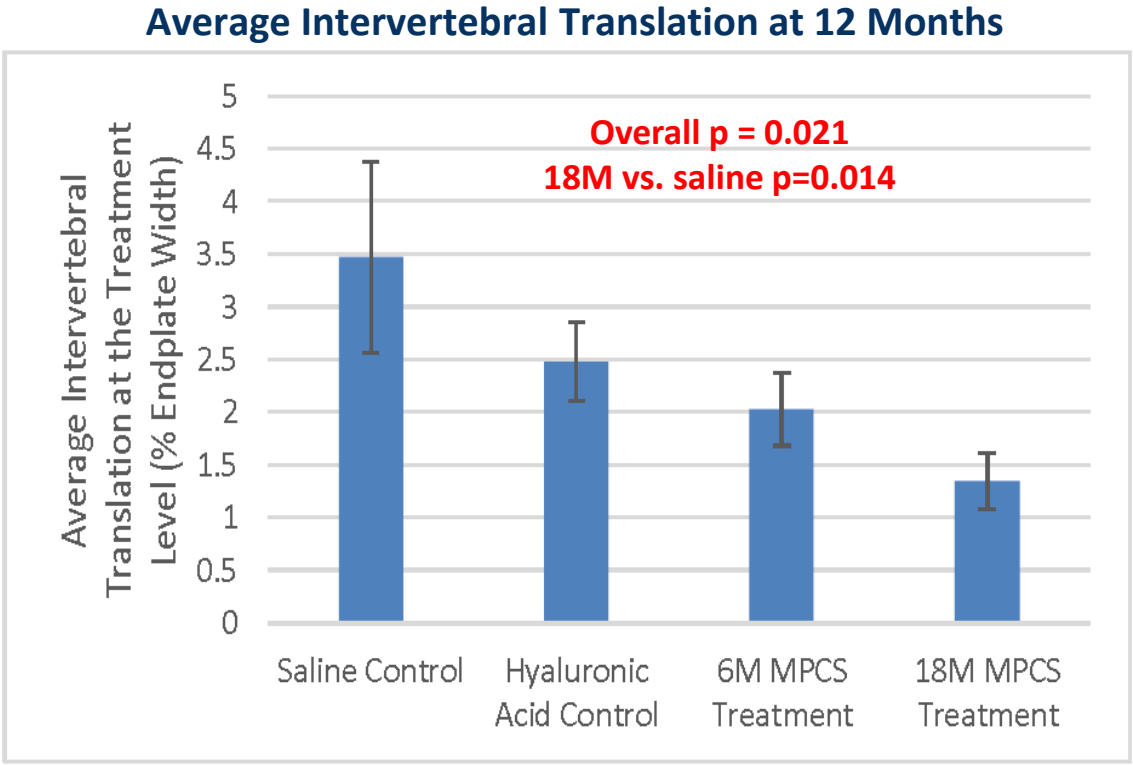
1 of 16 (6.25%) of Saline patients



4 of 17 (23.53%) of HA patients



MPCs treatment results in radiographic evidence of decreased intervertebral translational motion, a measure of the increased stability of the disc annulus[1]



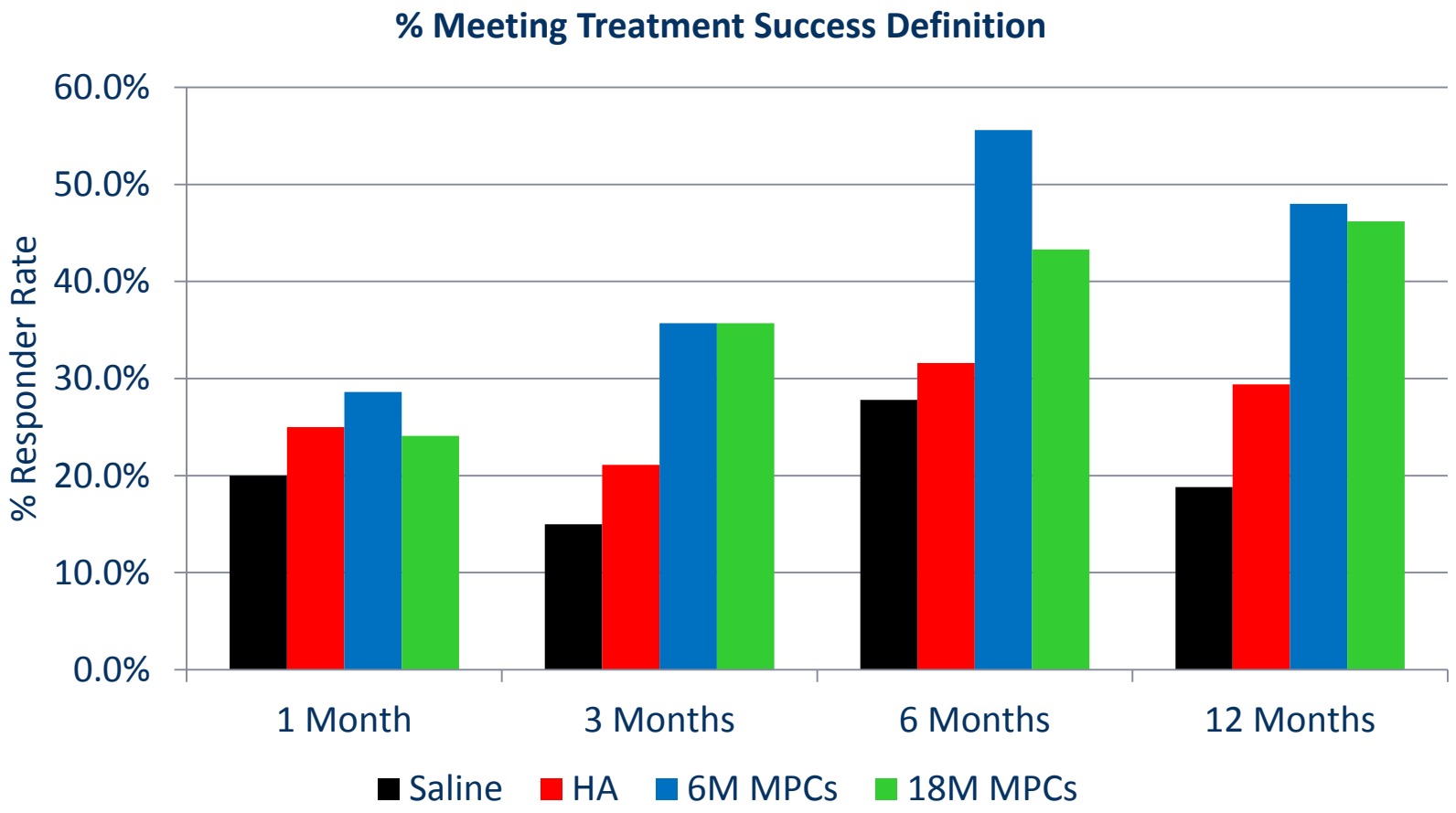
- The magnitudes of intervertebral rotation and translation that occurs in the sagittal plane between the flexed and extended positions are the most commonly used measures of spine motion
- Changes in translational motion correlate with disc stability in early disease (Pfirrmann Grade <5), as in this study population[1]
- There were no significant differences between groups at baseline for radiographic measurements or spinal motion, suggesting that the differences at 12 months reflect treatment related changes

[1] *Inoue et al. Othop Clin N Am 42 (2011) 487-499*

Composite Endpoint for Treatment Success

50% VAS back pain reduction; AND 15 point ODI improvement;
AND no intervention at the treated level

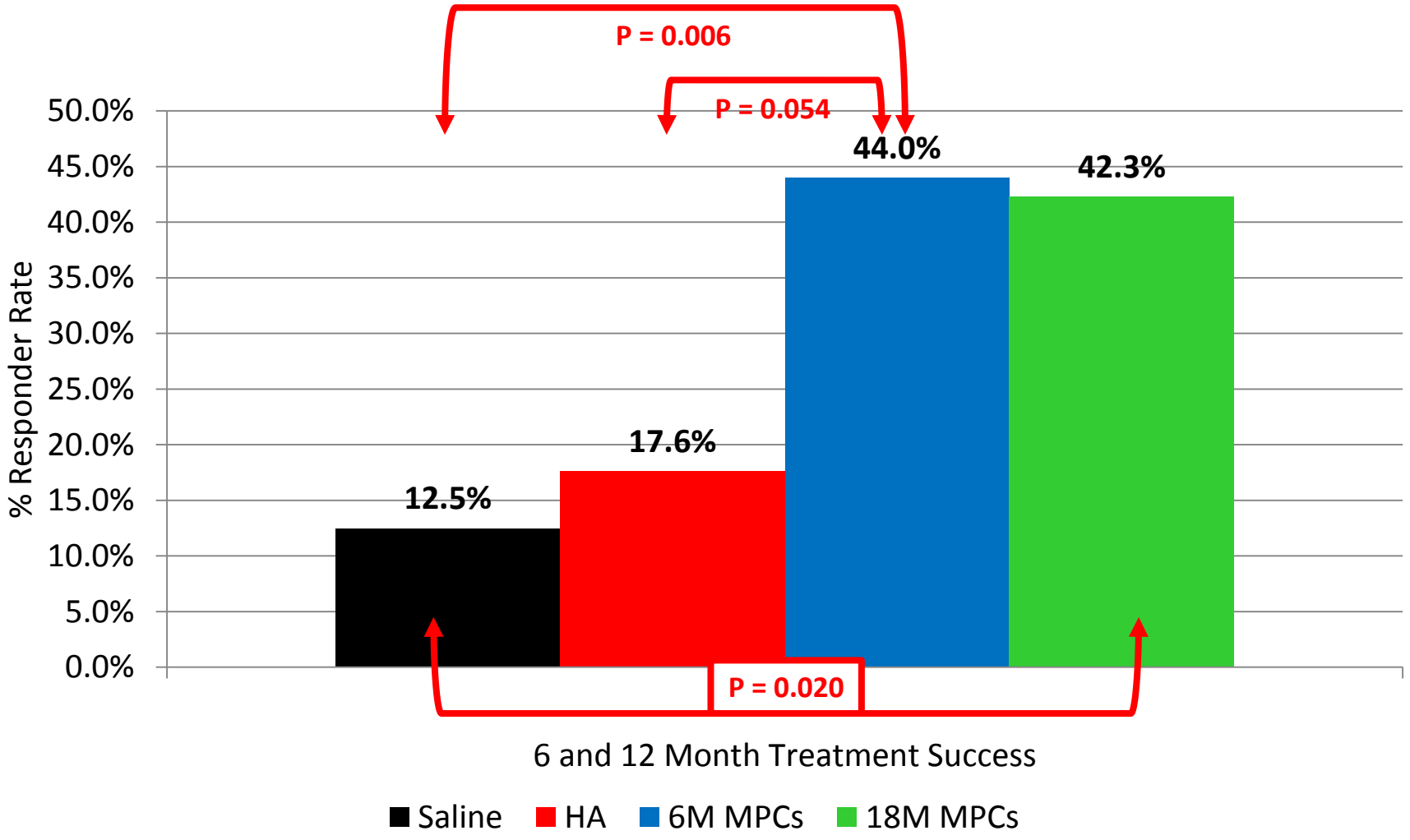
MPCs groups show sustained treatment effect relative to controls over 12 months



MPC treated groups have significantly greater numbers of patients with treatment success at both 6 & 12 months

Treatment Success Over 12 Months

50% VAS back pain reduction AND 15 point ODI improvement AND no intervention at the treated level at both 6 and 12 months



Conclusion

- Allogeneic MPCs were well tolerated
- Both MPC doses showed improvement relative to controls for pain and functional improvement and reduced interventions
- Radiographic improvement in disc motion suggests improvement in disc structure and stability
- Over three fold increase in the number of MPC treated patients achieving concordant pain and function treatment success at both 6 and 12 months relative to saline controls
- Next steps: Randomized, placebo controlled phase 3 trials comparing 6M MPCs to saline placebo