Next Generation Orthobiologic Therapy for Chronic Lumbar Disc Disease: Initial Phase 2 Data of Hypoxic Cultured Mesenchymal Stem Cells

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Back Pain

Conservative Treatments

ORAL MEDICATION TREATMENT / OPIOIDS

$1,000 - $2,000 / annually

INJECTION TREATMENT

$8,000 / annually

$2,000 per injection, 2 injections per treatment-semi-annual treatment

PHYSICAL MEASURES

$20,000 / annually

$200 per session, 2 sessions per week

Often Recurrent

NON-INVASIVE

Orthobiologics

Introduce Hypoxic Cultured Autologous MSCs

BRTX-100

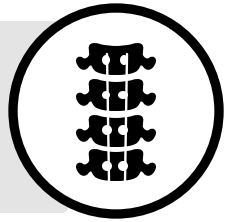
SINGLE INTRA-DISCAL INJECTION
EXACTLY 40MM CELLS
PROCEDURE TIME ~ 20 minutes

NON-INVASIVE

Surgical Treatments

SPINAL FUSION SURGERY

$110,000



DISCECTOMY

$20,000 - $50,000

DISC REPLACEMENT SURGERY

$80,000 - $150,000

Re-op Rates Often >30%

INVASIVE

Targeting Disc Microenvironment

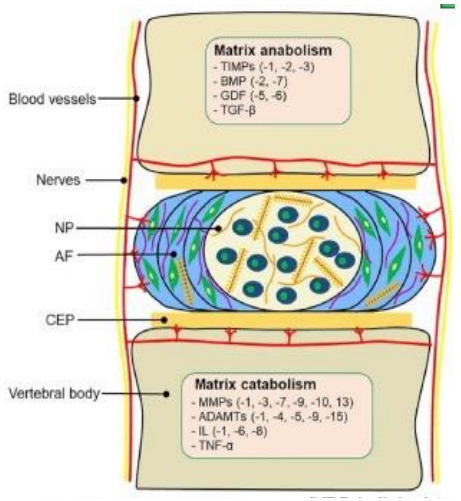
HYPOXIA

⬆ NP Cellularity
Notochord/Chondrocyte Cells
Sox9,ACAN,BGLAP,ALPL,KRT19,BARX1,MDFI,DCHS1,TGFB3, BMP-4,GDF-5,VEGF

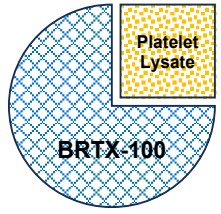
⬆ Vasculogenesis & Angiogenesis
VEGF,FGF1,TGFB1,MDK,GRN,SPHK1,Desmin,RASIP1,LYL1,TXNIP,FES

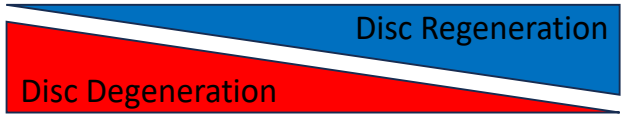
⬇ Inflammation & Poorly Immunogenic
SFN,TNFAIP6,Low CXCL5, Low chemokines

⬆ Tissue Remodeling & Regeneration
SFN,DES,ACAN,TIMP 1/3,ADAMTS4,MMP2, ANKH

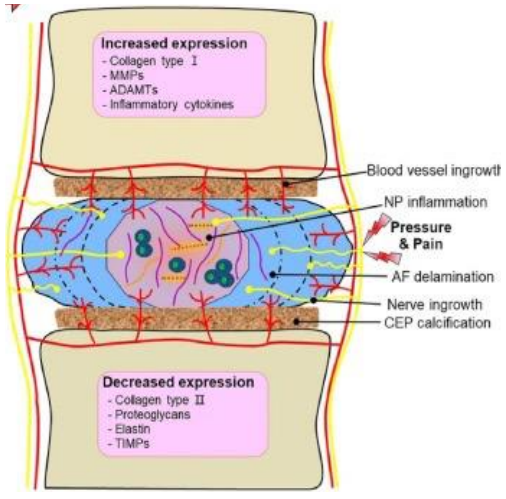


Cellular Survival, Migration & Proliferation
GPX3,LYL1,FES,AP AG4,ACTG2,TXNIP



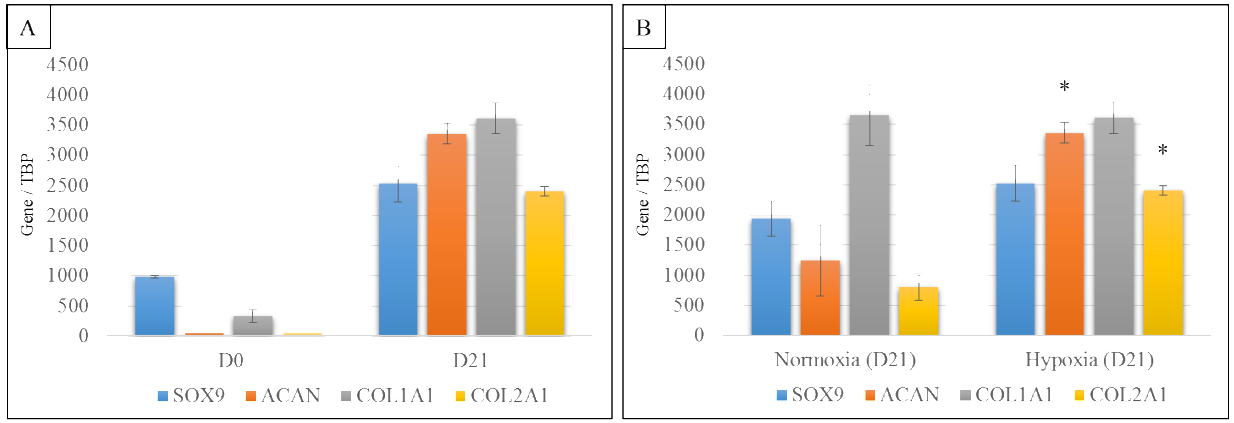


Inflammation
Cellularity (Notochord/Chondrocyte)
NP Matrix
Scar Tissue
NP Hydration
Blood/Nutrient Flow

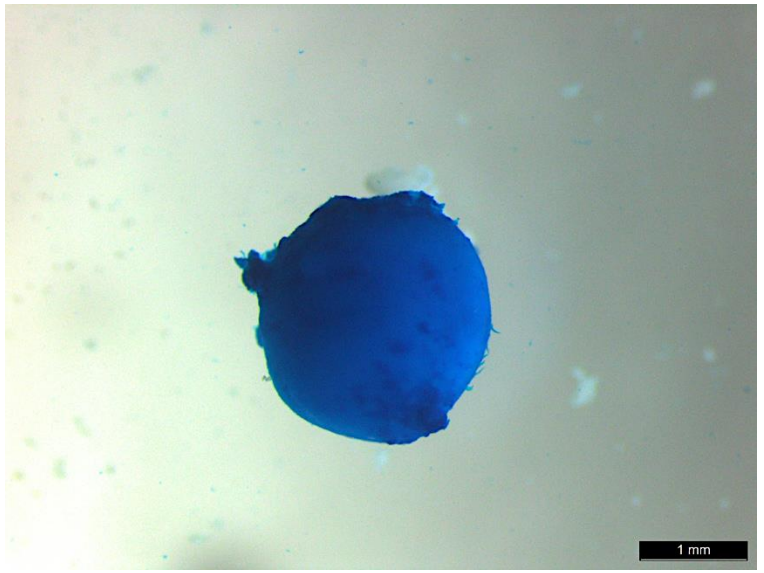


BRTX-100 Hypoxic BM-MSCs

Figure 1. Chondrocyte Differentiation



Expression of SOX9, Aggrecan (ACAN), Collagen Type I Alpha 1 Chain (COL1A1) and Collagen Type II Alpha 1 Chain (COL2A1) by qPCR. A) Hypoxic cultured bone marrow derived mesenchymal stem cells (HC-BMMSCs) at day 0 (D0, undifferentiated) and 21 days after chondrocyte differentiation (D21). B) HC-BMMSC versus Normoxic cultured-BMMSC 21 days after chondrocyte differentiation. Data represent mean +/- SEM (n = 3 donor-matched hypoxic and normoxic samples).



BRTX-100 Hypoxic BM-MSCs

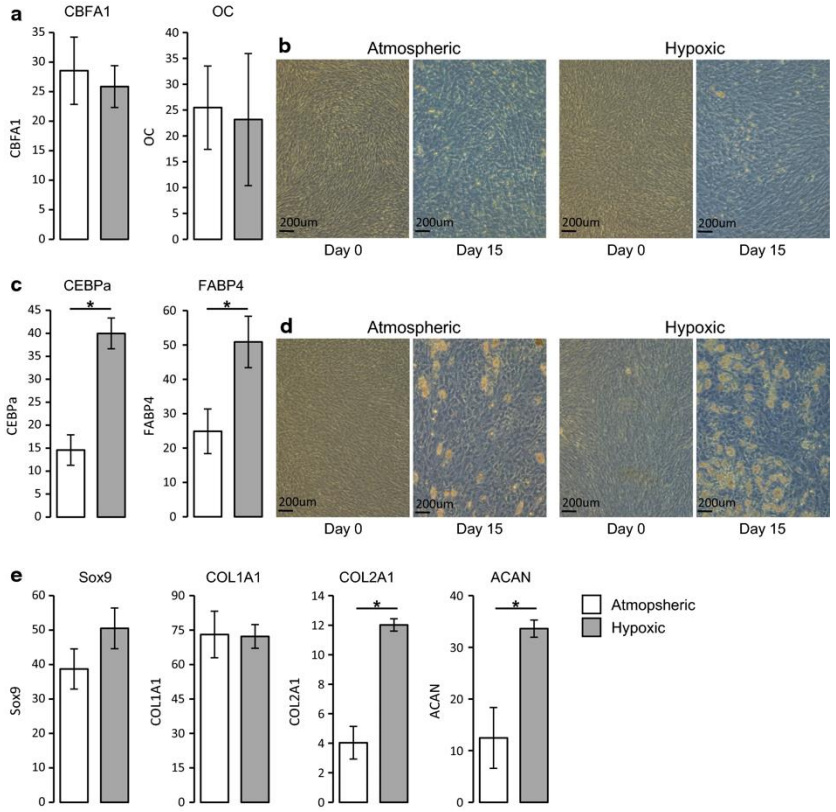
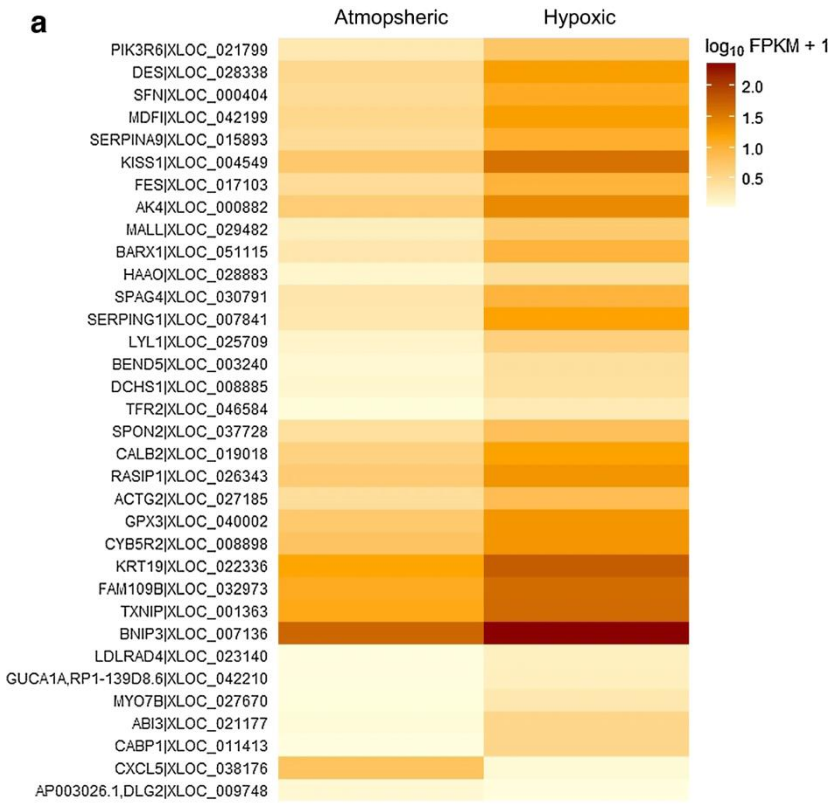


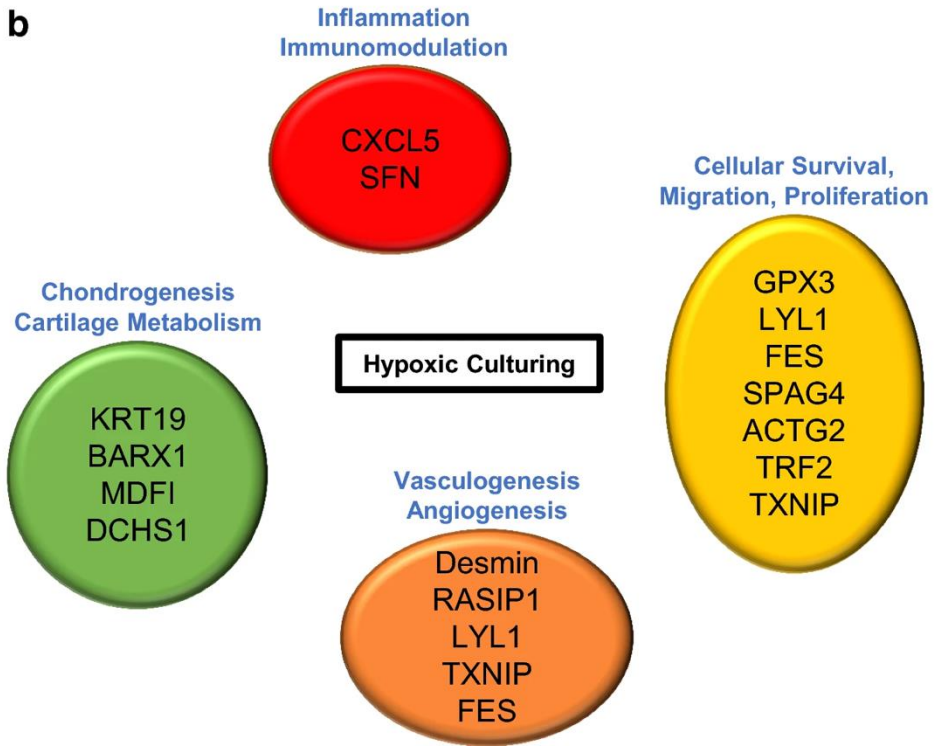
Table 1. Chondrogenic Growth Factor and Notochord Transcripts Expressed by HC-BMMSCs

Human Notochord Markers	Hypoxia (H) Value (FPKM)	Normoxia (N) Value (FPKM)	Fold Difference H versus N
KRT19	57.12	14.18	4.03
KRT18	40.21	14.57	2.76
LGALS3 (GLA3/Galectin-3)	105.20	88.64	1.19
CD55	3.47	4.67	-1.35
BASP1	109.85	111.65	-1.02
CTGF	262.25	260.07	1.01
CA12	100.51	88.61	1.13
ANXA2	2619.54	2616.84	1.00
Growth Factors Involved in Chondrogenesis			
TGFB3	2.01	3.09	-1.53
FGF-2	1.35	2.37	-1.76
BMP-4	5.68	8.00	-1.41
GDF-5	42.63	38.47	1.11
PTHLH (PTHrP)	2.19	0.92	2.38
VEGF	97.95	90.91	1.08

Gene expression by RNA sequencing of donor matched HC-BMMSC and NC-BMMSC. FPKM (Fragments Per Kilobase of Exon Per Million Fragments Mapped). HC-BMMSCs are presented in the "hypoxia" column and are compared to cells cultured under normoxic conditions. The FPKM value cut off for transcripts expression is set to values superior or equal to 1 (any value under 1 is considered not expressed). n = 3 donor-matched hypoxic and normoxic samples.

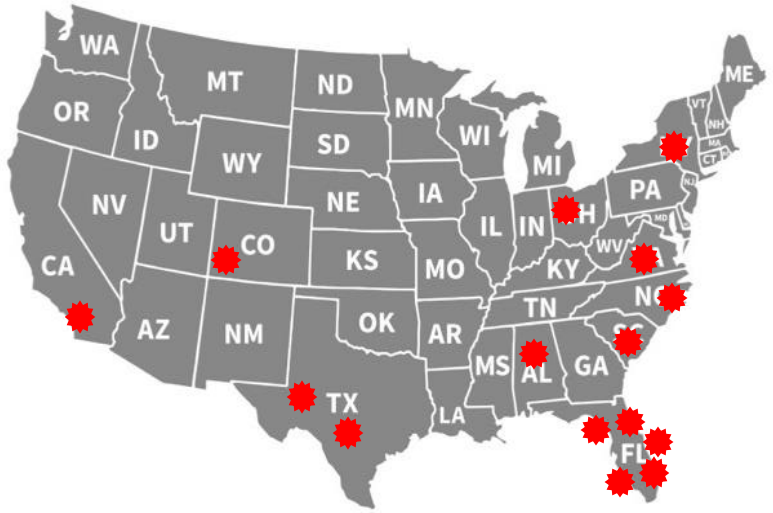
BRTX-100 Hypoxic BM-MSCs



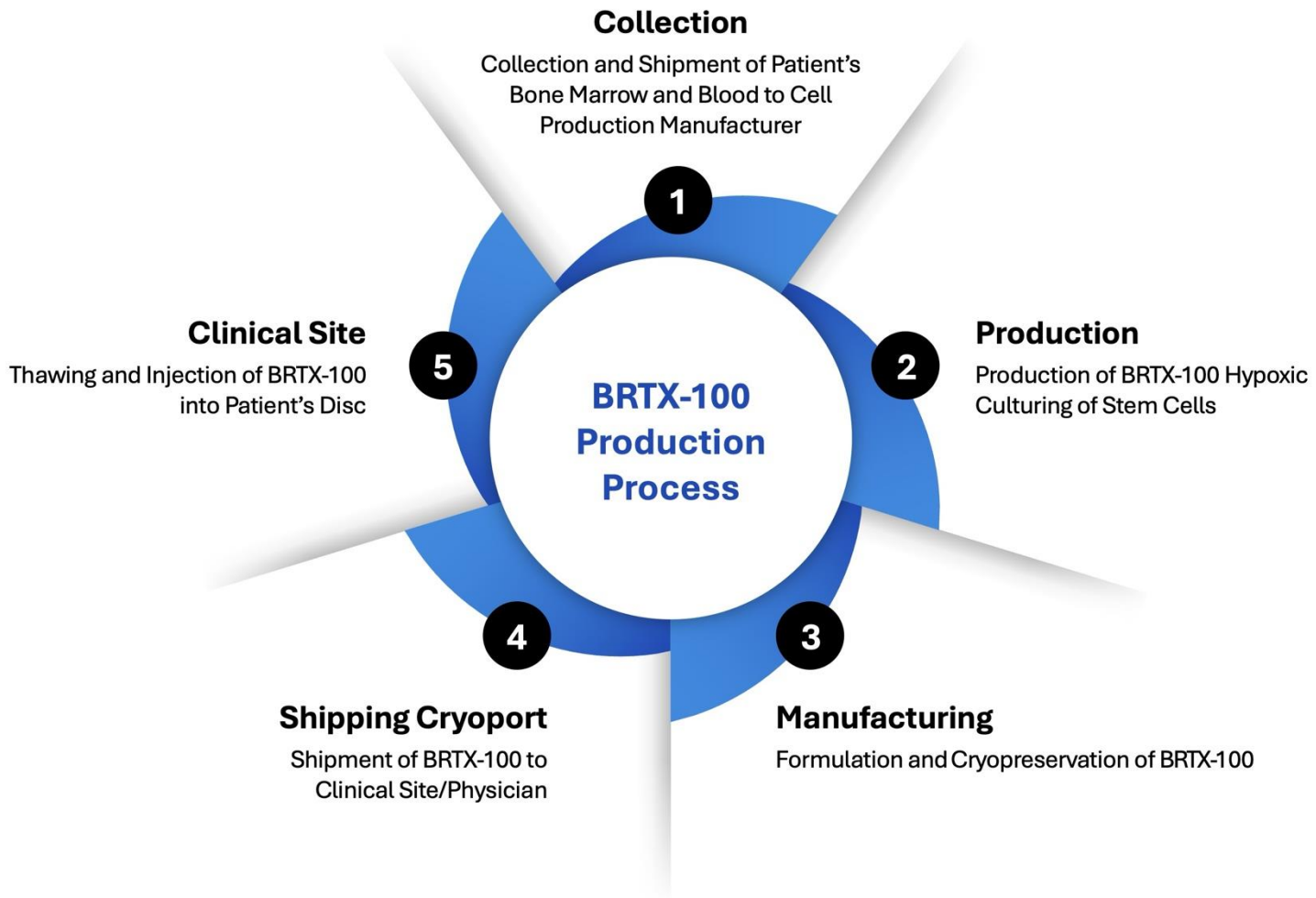


Phase 2 Clinical Trial – BRTX-100/IND 17275

- **A Phase 2, Double-Blind, Sham-Controlled, Randomized Study to Evaluate the Safety and Preliminary Efficacy of a Single Dose Intradiscal Injection of BRTX-100 for Patients with Chronic Lumbar Disc Disease (cLDD)**
  - BRTX-100 ($40x10^6$/1.5cc)
    - Hypoxic preconditioned
    - Targeted to avascular zones
  - 99 Subjects randomized 2:1
  - 16 active U.S. clinical sites U.S.



Phase 2 Clinical Trial – BRTX-100/IND 17275



Phase 2 Clinical Trial – BRTX-100/IND 17275

- **Double-blind, sham-controlled, randomized study with blinded assessments using a single dose.**
  - BRTX-100 ($40x10^6$/1.5cc)
- **Primary Objective: Safety**
  - To investigate the safety of a single dose of BRTX-100 via intradiscal injection in patients with chronic lumbar disc disease

Measured by the following Endpoints

- ❖ Report of adverse events (AEs), clinical review and questionnaires for pain, disability and quality of life at Baseline, **Week 2, Week 12, Week 26, Week 52**, and **Week 104**
- ❖ Vital Signs
- ❖ Physical Examination
- ❖ Laboratory Evaluation (hematology and chemistry)
- ❖ Clinical review of MRI changes from Baseline to Week 104 (MRI density measurements in T2 weighted images performed at Baseline, Week 52 and Week 104)

Phase 2 Clinical Trial – BRTX-100/IND 17275

- **Secondary Objective:**
  - To investigate the preliminary efficacy of single dose of BRTX-100 delivered via intradiscal injection in patients with chronic lumbar disc disease
- **Preliminary Primary Efficacy Endpoint**
  - **Clinical Response at Week 52**
    - At least a ***30% decrease in pain*** as measured on the VAS – Pain scale

      AND

    - At least a ***30% increase in function*** based on the Oswestry Disability Index

- **Secondary Efficacy Endpoints**
  - **Clinical Response** at Weeks 26 and 104
  - **VAS – Pain:** Δ from BL in pain based at Weeks 2, 12, 26, 52 and 104
  - **ODI:** Δ from BL in function at Weeks 2, 12, 26, 52 and 104
  - **RMDQ:** Δ from BL in function at Weeks 2, 12, 26, 52 and 104
  - **FRI:** Δ from BL in function at Weeks 2,12, 26, 52 and 104
  - **SF-12v2:** Δ from BL in quality of life at Weeks 2, 12, 26, 52 and 104

Phase 2 Clinical Trial – BRTX-100/IND 17275

- **Inclusion Criteria:**
  - High index of suspicion **degenerative disc disease** (DDD)/**discogenic pain**
    - Chronic lower back pain for at least 6 mos
    - Failure of at least 6 mos of conservative back pain care
    - Modified Pfirrmann score of 2 to 7 on MRI, may contain a contained protrusion and/or annular tear on MRI
    - Modic Grade I or II changes, or no change on MRI
    - Maintained intervertebral disc heights of at least 50% on MRI
    - Screening score of ≥ 40 mm and ≤ 80 mm on low back pain VAS
    - Screening Oswestry Disability Index score ≥ 30 and < 90 on a 100-point scale

- **Exclusion Criteria:**
  - High index as relating to underlying spine pathology
    - Acute or chronic **L/S spine fracture**
    - Clinically significant nerve or sacroiliac joint pain
    - Clinically significant facet pain as determined by a diagnostic medial branch block or facet joint injection
    - **Disc extrusions, sequestered frags, facet cysts, > moderate stenosis**
    - **Grade V annular fissure** **Modified Pfirrmann Grade 8**
    - **Previous L/S spine surgery** or **therapeutic percutaneous disc intervention**
    - Previous **treatment with cellular or biological investigational therapy or device**

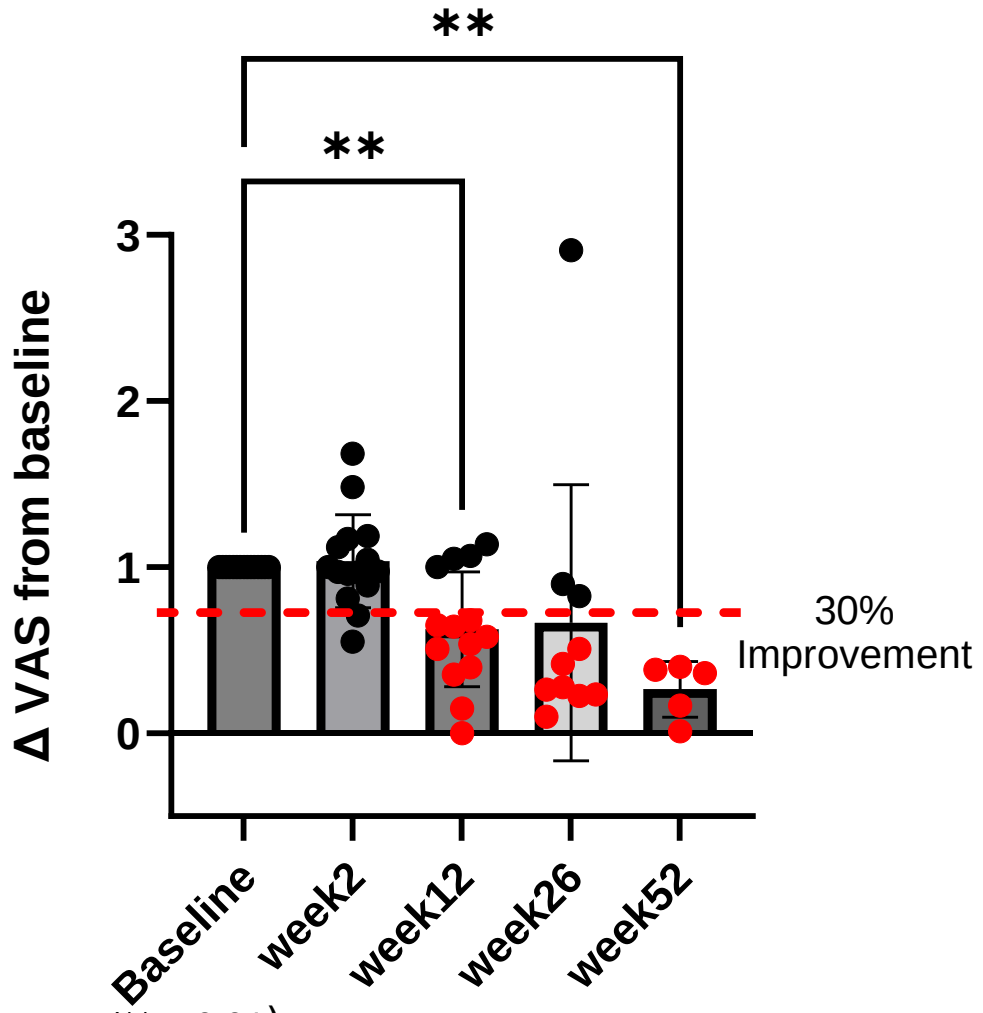
Phase 2 Clinical Trial – BRTX-100/IND 17275 Adverse Events

- **No serious adverse events (SAEs)**
- 9 adverse events (AEs) in 3 of the 10 safety run-in subjects
  - 5 AEs (2 subjects) related to treatment
    - 3 episodes of increased post-procedural back pain in 2 subjects
    - 2 MRI changes (worsening disc protrusion, acute Modic Type II changes) in 1 subject
  - 4 AEs (1 subject) unrelated to treatment
    - Ulnar nerve entrapment, trigger thumbs, trigger finger, non-alcoholic fatty liver disease in 1 subject

Good safety profile demonstrated in the first 10 subjects enrolled, passed DSMB safety review

Phase 2 Clinical Trial – BRTX-100/IND 17275 VAS

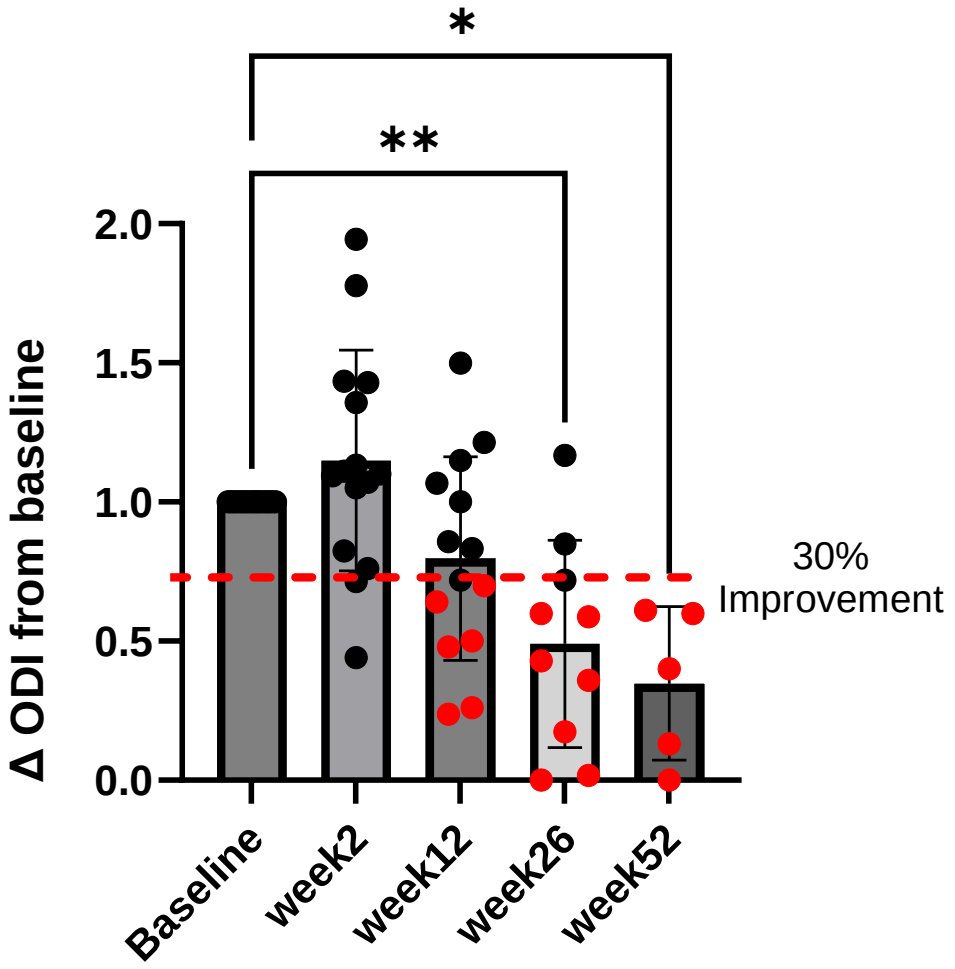
- At 26 weeks 70% of patients report > 30% improvement VAS score (n=10).
- At 52 weeks 100% of patients report > 30% Improvement VAS score (n=5)
- 12 week avg improvement > 30% = 51.70%
- 12 week avg improvement < 30% = -6.38%
- 26 week avg improvement > 30% = 71.20%
- 26 week avg improvement < 30% = -54.42%
- 52 week avg improvement = 73.58%



Mixed-effects analysis, with Geisser-Greenhouse correction and Dunnett's multiple comparison test (**p<0.01)

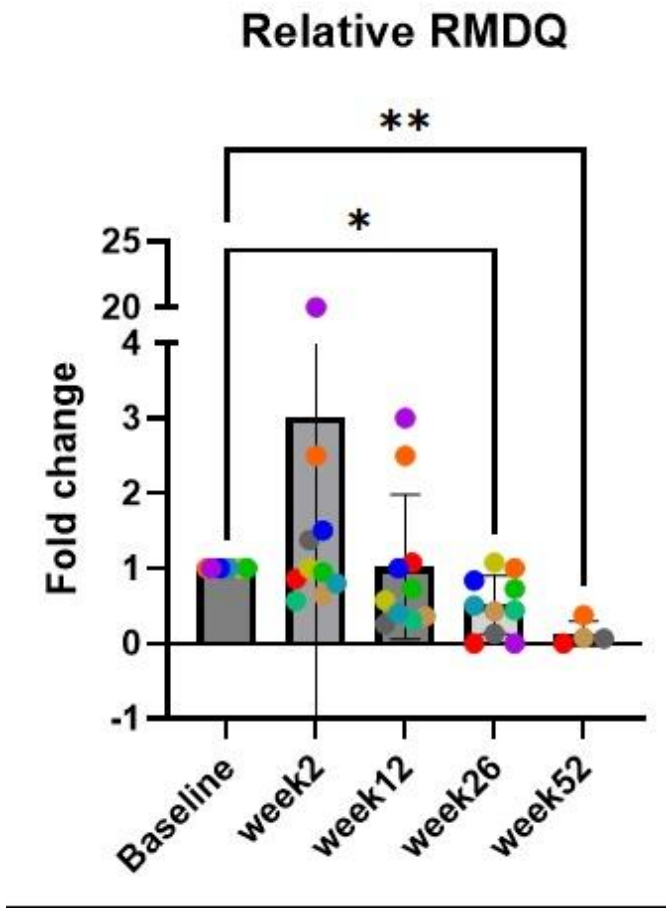
Phase 2 Clinical Trial – BRTX-100/IND 17275 ODI

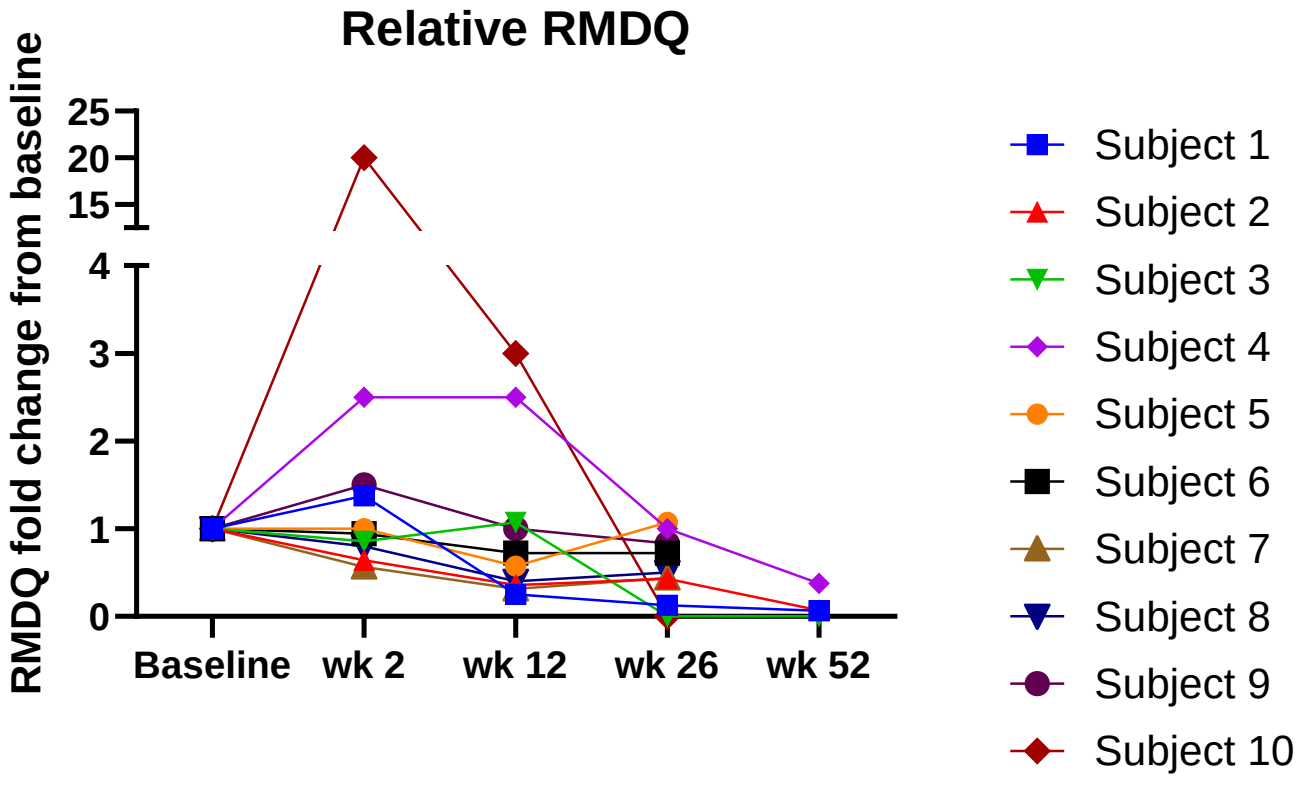
- At 12 & 26 weeks 70% of patients had >30% improvement in reported ODI from their baseline (n=10).
- At 52 weeks all patients reported greater than 30% improvement in reported ODI (n=5)
- 12 week avg improvement > 30% = 43.63%
- 12 week avg improvement < 30% = -10.8%
- 26 week avg improvement > 30% = 69.04%
- 26 week avg improvement < 30% = 8.82%
- 52 week avg improvement = 65.16%



Mixed-effects analysis, with Geisser-Greenhouse correction and Dunnett's multiple comparison test (* p<0.05, **p<0.01)

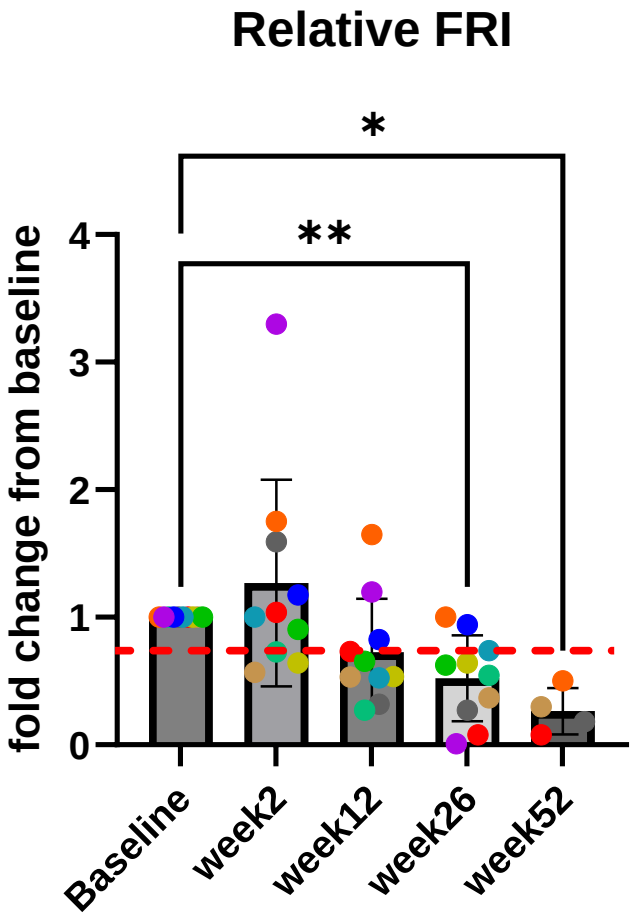
Phase 2 Clinical Trial – BRTX-100/IND 17275 RMDQ

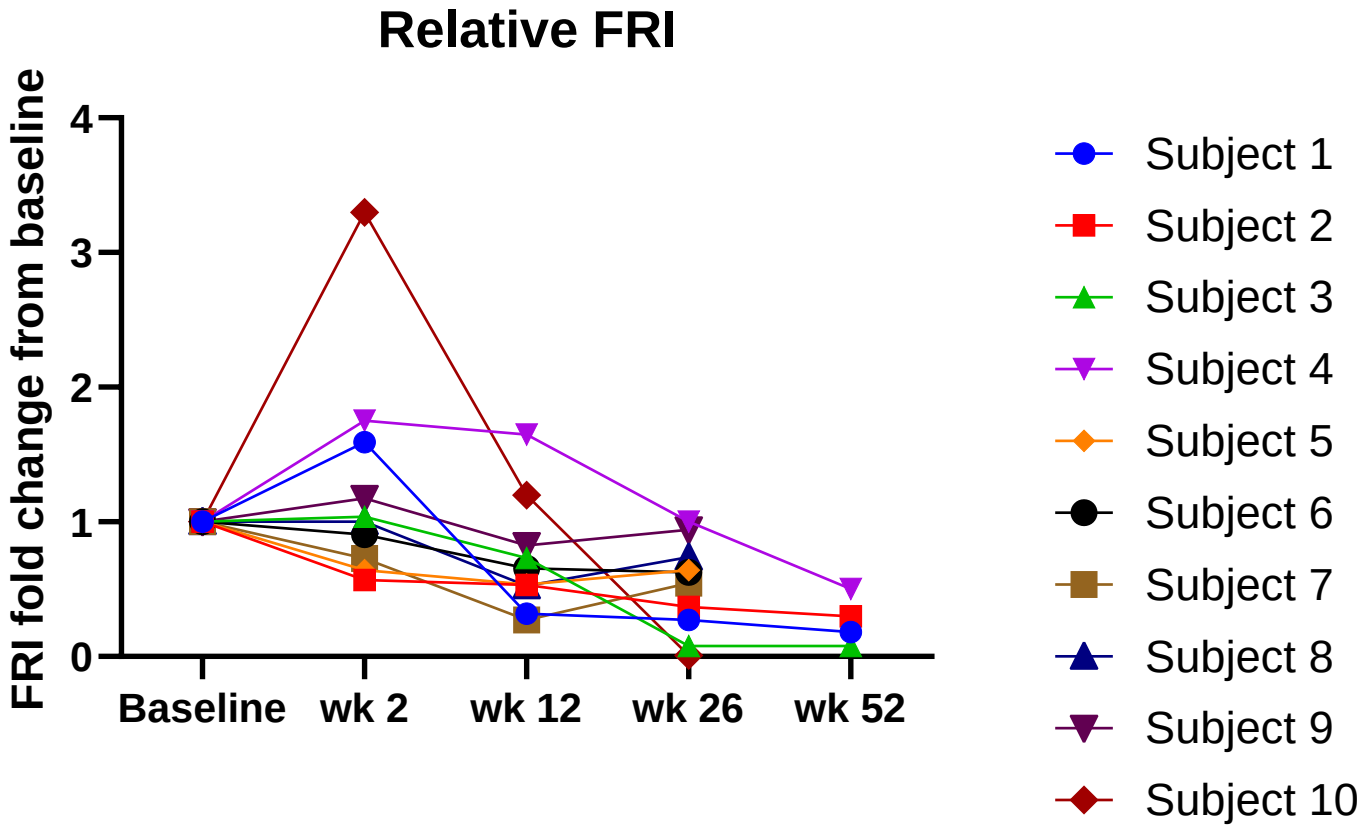




Mixed-effects analysis, with Geisser-Greenhouse correction and Dunnett's multiple comparison test (*p< 0.05, **p<0.01)

Phase 2 Clinical Trial – BRTX-100/IND 17275 FRI



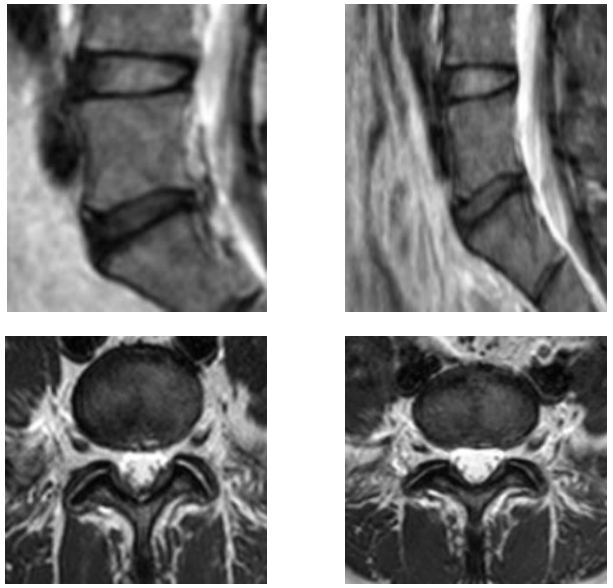


Mixed-effects analysis, with Geisser-Greenhouse correction and Dunnett's multiple comparison test (*p< 0.05, **p<0.01)

Phase 2 Clinical Trial – BRTX-100/IND 17275
MRI Baseline vs 52 Weeks

L5/S1 disc

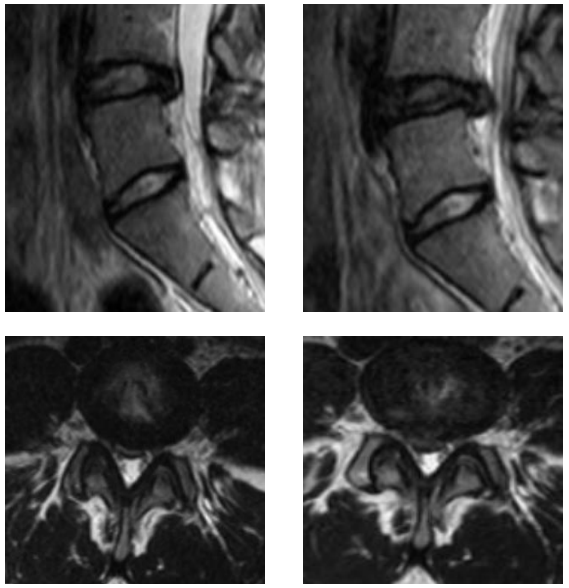
- Initial Screen vs 52 weeks:
- Increased T2 signal
- Decreased size protrusion
- Decreased annular tear signal



Baseline 52 weeks

L4/5 disc

- Initial Screen vs 52 weeks:
- Increase size of initial and more notable protrusion
- Evolution of an extruded disc lesion



Baseline 52 weeks

Phase 2 Clinical Trial – BRTX-100/IND 17275

- **Preliminary Safety End Points**
  - Blinded clinical data of a single dose of BRTX-100 ($40x10^6$) is well tolerated with no SAE or dose limiting toxicity at 26-52 weeks (n=15)
- **Preliminary Efficacy End Points**
  - Blinded clinical data of preliminary efficacy end points is encouraging
    - VAS and ODI 30% changes compared to baseline (MCID/Efficacy end point target)
    - 70% response rate trend
- **Potential Evidence of Disc Microenvironment Remodeling**
  - Blinded MRI data baseline vs 52 weeks
- **Potential interim analysis at 26 weeks to assess safety and preliminary efficacy end points**
- **Expansion of BRTX-100 to include cervical indications**

Next Generation Orthobiologic: BRTX-100

Thank you!