A Small Molecule Inhibitor of the Wnt Pathway (SM04690) as a Potential Treatment for Degenerative Disc Disease

**Background**

- Degenerative disc disease (DDD), a major cause of low back pain, is characterized by degeneration of intervertebral discs (IVDs), which are composed of central nucleus pulposus (NP) surrounded by collagenous annulus fibrosus (AF) and cartilaginous endplates.

- The NP contains progenitor cells that can differentiate into chondrocyte-like cells to form a proteoglycan and collagen-rich extracellular matrix (ECM), responsible for hydration and IVD function; loss of NP cellularity and hydration results in decreased disc height and function. 1,2

- Wnt signaling plays a key role in IVD development and growth. 3 Excessive Wnt signaling results in inhibition of NP cell proliferation, upregulation of pro-inflammatory cytokines and ECM degrading enzymes, and apoptosis of NP cells, which lead to DDD. 3,4,6

- Pharmacological treatment of DDD is limited to analgesics and/or surgery aimed at relieving symptoms and experimental biologic treatments with as yet unknown efficacy. 7 No current FDA approved therapy has been shown to reverse disc degeneration. 1

- SM04690, a potent small molecule Wnt pathway inhibitor, is being developed as a potential injectable therapeutic for the treatment of DDD.

**Methods**

- To identify Wnt signaling inhibitors, a small molecule chemical library was screened in a cellular Wnt pathway-based β-catenin/TFF-responsive reporter assay in SW846 colon cancer cells.

- Anti-inflammatory activity was evaluated by measuring a panel of secreted pro-inflammatory cytokines from peripheral blood mononuclear cells (PBMCs) stimulated with super-antigen (sAg) or IgM.

- Effects on fibrosis were assessed in TGF-β-stimulated human dermal fibroblasts (HDFs) by measuring smooth muscle actin (αSMA).

- In vitro proliferation of NP cells isolated from rat coccygeal discs, treated with vehicle or SM04690 for 5 days, was measured by cell doubling index (CDI = cell number/initial cell number/day).

- Differentiation of NP progenitor cells into chondrocyte-like NP cells following 12 days of vehicle or SM04690 treatment was measured by Alcian blue staining and absorbance based quantification.

- Pharmacokinetics was evaluated by intradiscal injection in rats and rabbits, followed by LC-MS analysis of compound concentrations in the disc and plasma.

- Rat coccygeal IVD needle puncture was used as a DDD model.
  - Injured discs were radiographed pre-surgery and 1 week (immediately prior to dosing), 4 weeks, and 6 weeks post-surgery.
  - Saffranin-O/Fast Green or Masson's Trichrome stained discs were histologically evaluated by blinded observers using a disc scoring system based on grading of the integrity of AF, border between AF and NP, and cellularity and matrix of NP. Disc height index (DHI) was calculated by averaging the anterior, middle, and posterior portions of the disc height and dividing by the average height of the adjacent vertebral body.

**Results**

- SM04690 demonstrated potent inhibition of Wnt signaling.
- SM04690 inhibited T and B cell inflammatory responses in co-culture systems.

**Conclusions**

- SM04690, a small molecule inhibitor of the Wnt signaling pathway, demonstrated potent anti-inflammatory and anti-fibrotic activity in vitro.

- SM04690 induced the proliferation and differentiation of NP-derived progenitor cells in vitro.

- A single intradiscal injection of SM04690 had sustained residence time in the disc and minimal systemic exposure in rats.

- In a rat model of DDD, a single intradiscal injection of SM04690 improved disc height, health, and shape after injury in vivo compared with vehicle controls.

- SM04690 improved the NP and IVD structure in this in vivo model of DDD compared with vehicle control.

- SM04690 has potential as a regenerative treatment for DDD.

- SM04690 was approved for clinical development (clinicaltrial.gov identifier NCT013246399).

**References**